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(54) **TAXOL ENHANCER COMPOUNDS**

VERBINDUNGEN MIT TAXOL-VERSTÄRKENDER WIRKUNG

COMPOSES ACTIVATEURS DE TAXOL

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WO-A-94/10995 **WO-A-99/34796**

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- **STALTERI M.A. ET AL.: "Site-Specific Conjugation and Labeling of Prostate Antibody 7E11C5.3 (CYT-351) with Technetium-99m" EUROPEAN JOURNAL OF NUCLEAR MEDICINE, vol. 24, no. 6, 1997, pages 651-654, XP001117543**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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Description

BACKGROUND OF THE INVENTION

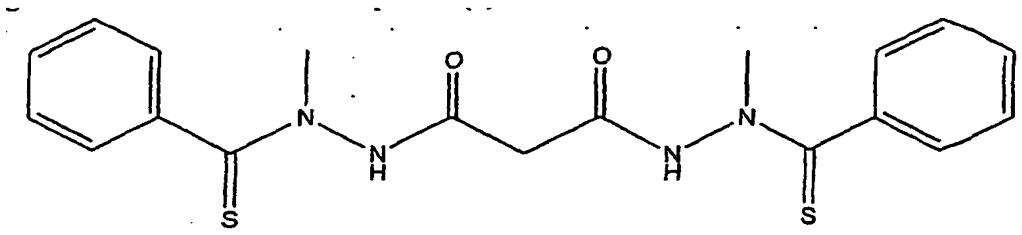
[0001] Many new drugs are now available to be used by oncologists in treating patients with cancer. Often, tumors are more responsive to treatment when anti-cancer drugs are administered in combination to the patient than when the same drugs are administered individually and sequentially. One advantage of this approach is that the anti-cancer agents often act synergistically because the tumors cells are attacked simultaneously with agents having multiple modes of action. Thus, it is often possible to achieve more rapid reductions in tumor size by administering these drugs in combination. Another advantage of combination chemotherapy is that tumors are more likely to be eradicated completely and are less likely to develop resistance to the anti-cancer drugs being used to treat the patient.

[0002] One serious limitation of combination chemotherapy is that anti-cancer agents generally have severe side effects, even when administered individually. For example, the well known anti-cancer agent taxol causes neutroperia, neuropathy, mucositis, anemia, thrombocytopenia, bradycardia, diarrhea and nausea. Unfortunately, the toxicity of anti-cancer agents is generally additive when the drugs are administered in combination. As result, certain types of anti-cancer drugs are generally not combined. The combined toxic side-effects of those anti-cancer drugs that are administered simultaneously can place severe limitations on the quantities that can be used in combination. Often, it is not possible to use enough of the combination therapy to achieve the desired synergistic effects. Therefore, there is an urgent need for agents which can enhance the desirable tumor attacking properties of anti-cancer agents without further increasing their undesirable side-effects.

[0003] Antitumor synergistic compositions comprising taxol or and of its derivatives along with another compound are known e.g. from WO-A-94/10995 and WO-A-99/34796.

SUMMARY OF THE INVENTION

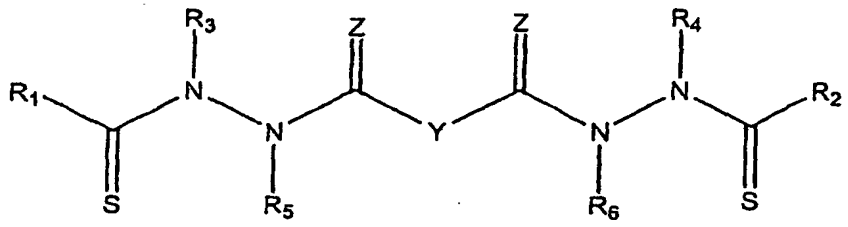
[0004] It has now been found that certain bis[thio-hydrazide amide] compounds significantly enhance the anti-cancer activity of taxol. For example, Compound (1) was used in combination with taxol (Paclitaxel) to treat tumors induced in nude mice from the human breast tumor cell line MDA-435. The tumor volume was about five fold less after 24 days of treatment in mice which had been administered 5 mg/kg of taxol and 25 mg/kg of Compound (1) than in mice which had only been administered 5 mg/kg of taxol or in mice which had only been administered 50 mg/kg of Compound (1) (Example 13). These results are shown graphically in Figure 1. The structure of Compound (1) is shown below:



Compound (1)

It has also been found that these bis[thio-hydrazide amide] compounds have minimal toxic side effects. For example, the mice treated with taxol and Compound (1) showed little if any weight loss over the treatment period (see Figure 2). Based on these results, novel compounds which enhance the anti-cancer activity of taxol, pharmaceutical compositions comprising these compounds and methods of treating a subject with cancer are disclosed herein.

[0005] One embodiment of the present invention is a compound represented by the Structural Formula (I):



(I).

[0006] Y is a covalent bond or a substituted or unsubstituted straight chained hydrocarbyl group. Preferably, Y is a covalent bond or -C(R_7R_8)-.

[0007] R_1 and R_2 are independently an aryl group or a substituted aryl group, R_3 and R_4 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group.

[0008] R_5-R_6 are independently -H or an aliphatic group.

[0009] R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8, taken together, are a C2-C6 substituted or unsubstituted alkylene group.

[0010] Z is =O or =S.

[0011] In one aspect, R_1 and R_2 in the compound represented by Structural Formula (I) are not both phenyl when Y is -C(R_7R_8)-, R_3 and R_4 are both phenyl and R_5-R_8 are all -H.

[0012] Another embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by Structural Formula (I). Preferably, the pharmaceutical composition comprises an effective concentration of the compound.

[0013] Yet another embodiment of the present invention is a method of treating a subject with cancer. The method comprises administering to the subject an effective amount of taxol or a taxol analog and an effective amount of a compound represented by Structural Formula (I).

[0014] The disclosed compounds increase the anti-cancer activity of taxol and taxol analogs. In addition, these compounds have minimal toxic side-effects. Consequently, it is possible to increase the effectiveness of taxol and analogs thereof when used in combination with the disclosed compounds, even when approaching the highest tolerated doses of taxol. Thus, it is expected that combination therapy with the compounds of the present invention will provide improved clinical outcomes for patients with cancers that are being treated with taxol. By coadministering the disclosed compounds with taxol, it is also possible to achieve the same therapeutic effectiveness previously achieved with higher doses of taxol, thereby reducing the side-effects and improving the quality of life for the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

Figure 1 is a graph showing the average tumor volume in milliliters over time (in days) in nude mice treated with vehicle; Compound (1) (50 mg/kg); Paclitaxel (5 mg/kg); Compound (1) (25 mg/kg) and Paclitaxel (5 mg/kg); or Compound (1) (50 mg/kg) and Paclitaxel (5 mg/kg). The tumors were generated from the human breast tumor cell line MDA-435.

Figure 2 is a graph showing the percent weight change over time in nude mice treated with vehicle; Compound (1) (50 mg/kg); Paclitaxel (5 mg/kg); Compound (1) (25 mg/kg) and Paclitaxel (5 mg/kg); or Compound (1) (50 mg/kg) and Paclitaxel (5 mg/kg). The mice were being treated for tumors generated from the human breast tumor cell line MDA-435.

Figure 3 is the structure of taxol (Paclitaxel)

Figure 4 is the structure of taxotere (Docetaxel)

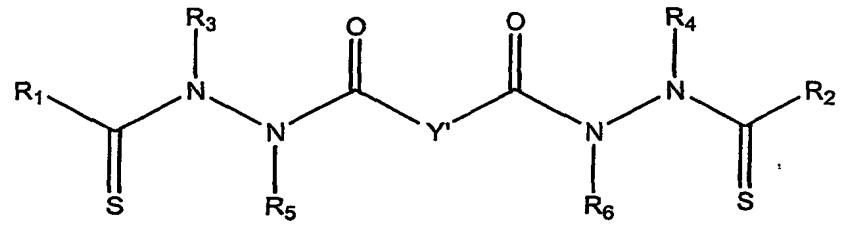
Figures 5-25 are each the structure of a taxol analog.

Figure 26 is the structure of a polymer comprising a taxol analog group pendent from the polymer backbone. The polymer is a terpolymer of the three monomer units shown.

DETAILED DESCRIPTION OF THE INVENTION

[0016] In a first preferred embodiment, Y in Structural Formula (I) is a covalent bond or a substituted or unsubstituted straight chained hydrocarbyl group. R_7 and R_8 are as described for Structural Formula (I). Preferably, Y is a covalent bond, - $C(R_7R_8)$-, -(CH_2CH_2)-, *trans*-(CH=CH)-, *cis*-(CH=CH)-, -(CC)- or a 1,4-phenylene group. Even more preferably, Y is a covalent bond or -$C(R_7R_8)$-.

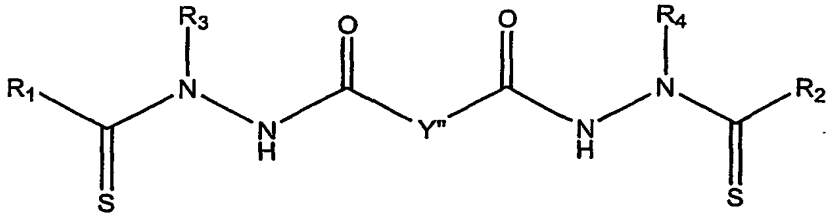
[0017] In a second preferred embodiment, Y in Structural Formula (I) is a covalent bond or -$C(R_7R_8)$- and the compound of the present invention is represented by Structural Formula (III):



(III).

R_1-R_8 are as described for Structural Formula (I). Y' is a covalent bond or -$C(R_7R_8)$-Preferably, R_7 and R_8 are both methyl; R_7 and R_8, taken together, are propylene or butylene; or R_7 is -H and R_8 is lower alkyl (preferably methyl), thienyl, phenyl, benzyl, or amino.

[0018] In a more preferred embodiment, R_5-R_8 in Structural Formula (III) are -H and the compound is represented by Structural Formula (IV):



(IV).

R_1-R_4 in Structural Formula (IV) are as described in Structural Formula (I). Y" is a covalent bond or -CH_2-.

[0019] In a first example of a compound represented by Structural Formula (IV), R_3 and R_4 are both a substituted or unsubstituted aliphatic group, preferably both a substituted or unsubstituted lower alkyl group and more preferably both a methyl group or ethyl. When R_3 and R_4 in Structural Formula (IV) are both a substituted or unsubstituted aliphatic group, then R_1 and R_2 are preferably both a substituted or unsubstituted aryl group (e.g., a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted phenyl group, or a phenyl group with at least one substituent other than an aliphatic group).

[0020] In a second example of a compound represented by Structural Formula (IV), R_3 and R_4 are both a substituted or unsubstituted heteroaryl group. When R_3 and R_4 in Structural Formula (IV) are both a substituted or unsubstituted heteroaryl group, then R_1 and R_2 are preferably both: 1) a substituted or unsubstituted phenyl group; or 2) a substituted or unsubstituted heteroaryl group.

[0021] In a third example of a compound represented by Structural Formula (IV), R_3 and R_4 are both a substituted or unsubstituted phenyl group (e.g., a phenyl group substituted with at least one group other than an aliphatic group). When R_3 and R_4 in Structural Formula (IV) are both a substituted or unsubstituted phenyl group, then R_1 and R_2 are preferably both: 1) a substituted or unsubstituted phenyl group; or 2) a substituted or unsubstituted heteroaryl group.

[0022] In a fourth example of a compound represented by Structural Formula (IV), R_1 and R_2 are both a substituted or unsubstituted aryl group (e.g., a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted phenyl group or a phenyl group substituted with at least one group other than an aliphatic group). More preferably, R_3 and R_4 are both methyl and the remainder of the variables are as described above.

[0023] In a fourth preferred embodiment, the compound of the present invention is represented by Structural Formula (III), wherein at least one of R_1-R_4 is a heteroaryl group, a substituted heteroaryl group, or a phenyl group substituted with at least one group other than an aliphatic group. Preferably, R_5-R_8 are all -H.

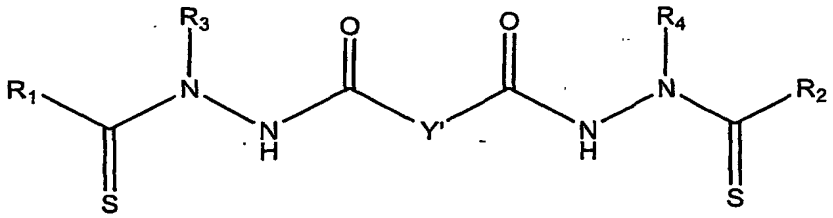
[0024] The following are specific examples of compounds represented by Structural Formula (IV): R_1 and R_2 are both phenyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both *o*-$CH_3C(O)O$-phenyl, and R_3 and R_4 are phenyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both n-propyl; R_1 and R_2 are both *p*-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *p*-nitro phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both n-butyl; R_1 and R_2 are both *p*-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-nitrophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-fluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-furanyl, and R_3 and R_4 are both phenyl;

R_1 and R_2 are both 2-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,3-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 2,5-difluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dichlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethyl-phenyl, and R_3 and R_4 are both methyl;

R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both methyl;

R_1 and R_2 are both 3,6-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both 2-methyl-5-pyridyl, and R_3 and R_4 are both methyl; or R_1 is phenyl; R_2 is 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl.

[0025] In a fourth preferred embodiment, Y in Structural Formula (I) is -$C(R_7R_8)$- and R_5 and R_6 are both -H. When Y is a covalent bond or -CR_7R_8- and R_5 and R_6 are both -H, the compound of the present invention is represented by Structural Formula (V):



(V).

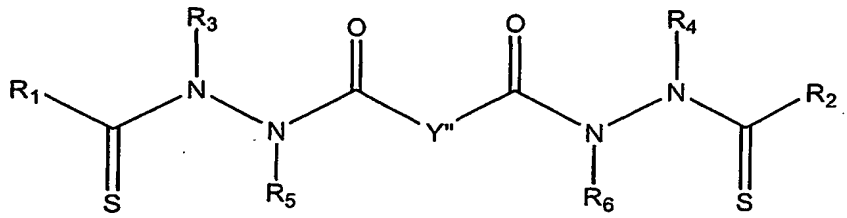
R_1-R_4, R_7 and R_8 are as described for Structural Formula (I) and Y' is a covalent bond or -CR_7R_8-. R_7 and R_8 are the same or different. Preferably, R_7 and R_8 are both methyl; R_7 and R_8, taken together, are propylene or butylene; or R_7 is -H and R_8 is lower alkyl (preferably methyl), thienyl, phenyl or benzyl.

[0026] In one example of a compound represented by Structural Formula (V), R_1 and R_2 are both aryl or substituted aryl groups and R_3 and R_4 are both a lower alkyl group or a substituted lower alkyl group; preferably, R_1 and R_2 are both aryl or substituted aryl groups, R_3 and R_4 are both methyl or ethyl, R_7 is -H and R_8 is -H or methyl. In another example of a compound represented by Structural Formula (V), R_1 and R_2 are both phenyl or substituted phenyl and R_3 and R_4 are both methyl, ethyl, phenyl, or thienyl. When R_1 and R_2 are both phenyl or substituted phenyl and R_3 and R_4 are both methyl, ethyl, phenyl, or thienyl, then preferably R_7 and R_8, taken together, are propylene or butylenes. In yet another example of a compound represented by Structural Formula (V), Y' is a covalent bond or -CR_7R_8-; R_1 and R_2 are both a substituted or unsubstituted aryl group; R_3 and R_4 are both -H, methyl or ethyl; and R_7 is -H and R_8 is -H or methyl.

[0027] The following are specific examples of compounds represented by Structural Formula (V): R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is ethyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both phenyl, and R_7 and R_8 are both methyl; R_1 and R_2 are both 2-thienyl; R_3 and R_4 are both phenyl, and R_7 and R_8 are both methyl; R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is benzyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is ethyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_7 is -H, and R_8 is n-butyl; R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is - H, and R_8 is methyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is *iso*-propyl; R_1 and R_2 are both 3-nitrophenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both

4-chlorophenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is 3-thienyl; R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl, and R_7 and R_8, taken together, are propylene; R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2-chloro-5-methoxy phenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2,6-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl; R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both ethyl; R_7 is -H, and R_8 is methyl, and R_1 and R_2 are both 2,5-diethoxyphenyl; R_3 and R_4 are both methyl; R_7 is -H, and R_8 is methyl.

[0028] In a fifth preferred embodiment, Y in Structural Formula (I) is a covalent bond or $-CH_2-$. When Y is a covalent bond or $-CH_2-$, the compound of the present: invention is represented by Structural Formula (VI):



(VI).

R_1-R_6 in Structural Formula (VI) are as described for Structural Formula (I). R_5 and R_6 are the same or different. Y" is a covalent bond or $-CH_2-$.

[0029] In one example of a compound represented by Structural Formula (VI), R_5 and R_6 are both a lower alkyl group (preferably methyl). When R_5 and R_6 are both a lower alkyl group, then R_1 and R_2 are preferably both phenyl or substituted phenyl and R_3 and R_4 are preferably both a lower alkyl group.

[0030] The following are more specific examples of compounds of the present invention: R_1 and R_2 are both phenyl, R_3 and R_4 are both phenyl, R_5 and R_6 are both methyl, and R_7 and R_8 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both phenyl, R_5 and R_6 are both *n*-hexyl, and R_7 and R_8 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 and R_6 are both methyl, and R_7 and R_8 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 and R_6 are both methyl, and R_7 is -H and R_8 is methyl; R_1 and R_2 are both 4-chlorophenyl, R_3 and R_4 are both methyl, R_5 and R_6 are both methyl, and R_7 and R_8 are both -H.

[0031] In Structural Formulas (I), (III- (VI), R_1 and R_2 are the same or different; and/or R_3 and R_4 are the same or different. Preferably, R_1 and R_2 are the same, and R_3 and R_4 are the same.

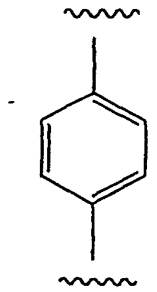
[0032] A "straight chained hydrocarbyl group" is an alkylene group, i.e., $-(CH_2)_x-$, with one or more (preferably one) methylene groups optionally replaced with a linkage group. x is a positive integer (e.g., between 1 and about 10), preferably between 1 and about 6 and more preferably 1 or 2. A "linkage group" refers to a functional group which replaces a methylene in a straight chained hydrocarbyl. Examples of suitable linkage groups include a ketone (-C(O)-), alkene, alkyne, phenylene, ether (-O-), thioether (-S-), or amine [-N(R^a)]-, wherein R^a is defined below. A preferred linkage group is $-C(R_7R_8)-$, wherein R_7 and R_8 are defined above. Suitable substitutents for an alkylene group and a hydrocarbaryl group are those which do not substantially interfere with the reactions described herein. R_7 and R_8 are preferred substituents for an alkylene or hydrocarbyl group.

[0033] An aliphatic group is a straight chained, branched or cyclic non-aromatic hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, and a cyclic aliphatic group has from 3 to about 10 carbon atoms, preferably from 3 to about 8. An aliphatic group is preferably a straight chained or branched alkyl group, e.g, methyl, ethyl, n-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with 3 to about 8 carbon atoms. A C1-C20 straight chained or branched alkyl group or a C3-C8 cyclic alkyl group is also referred to as a "lower alkyl" group.

[0034] Aromatic groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidy, pyranyl, pyrazolyl, pyrroyl, pyrazinyl, thiazole, oxazolyl, and tetrazole.

[0035] Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, quinolinyl, isoquinolinyl and isoindolyl.

[0036] The term "arylene" refers to an aryl group which is connected to the remainder of the molecule by two other bonds. By way of example, the structure of a 1,4-phenylene group is shown below:



Substituents for an arylene group are as described below for an aryl group.

[0037] Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Examples include tetrahydrofuranyl, tetrahyrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, and thiazolidinyl.

[0038] The terms "lower alkoxy", "lower acyl", "(lower alkoxy)methyl" and "(lower alkyl)thiomethyl" mean to -O-(lower alkyl), -C(O)-(lower alkyl), $-CH_2$-O-(lower alkyl) and $-CH_2$-S-(lower alkyl), respectively. The terms "substituted lower alkoxy" and "substituted lower acyl" mean -O-(substituted lower alkyl) and -C(O)-(substituted lower alkyl), respectively.

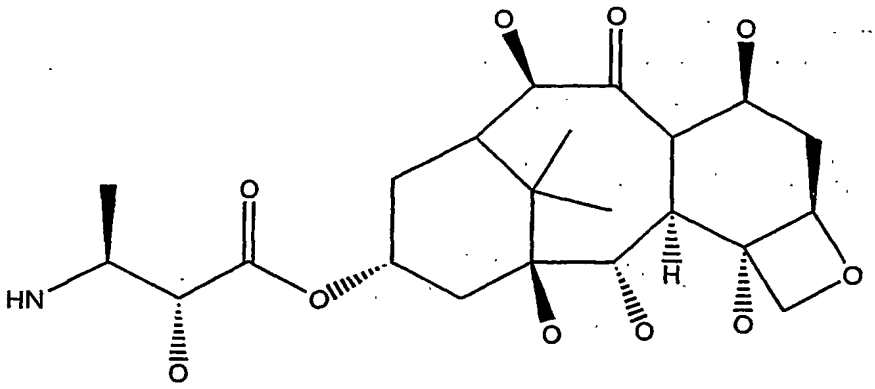
[0039] Suitable substituents on an aliphatic group, non-aromatic heterocyclic group. benzylic or aryl group (carbocyclic and heteroaryl) are those which do not substantially interfere with the ability of the disclosed compounds to enhance the anti-cancer activity of taxol and analogs thereof. A substituent substantially interferes with the ability of a disclosed compound to enhance anti-cancer activity when the enhancement is reduced by more than about 50% in a compound with the substituent compared with a compound without the substituent. Examples of suitable substituents include -OH, halogen (-Br, -Cl, -I and -F), $-OR^a$, -O-COR^a, - COR^8, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $N(R^aR^b)$, $-COOR^a$, -CHO, - $CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, - $NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, - $C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, - $NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, - NHR^aR^b, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, - $CR^c=CR^aR^b$,$-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SO_kR^a$ (k is 0, 1 or 2) and - NH-C(=NH)-NH_2. R^a-R^d are each independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group, preferably an alkyl, benzylic or aryl group. In addition, $-NR^aR^d$, taken together, can also form a substituted or unsubstituted non-aromatic heterocyclic group. A non-aromatic heterocyclic group, benzylic group or aryl group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted aliphatic group can also have a non-aromatic heterocyclic ring, a substituted a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A substituted aliphatic, non-aromatic heterocyclic group, substituted aryl, or substituted benzyl group can have more than one substituent.

[0040] Also included in the present invention are pharmaceutically acceptable salts of the compounds described herein. The compound of the present invention which possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid or acetic acid Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gammahydroxybutyrate, glycolate, tartrate, methanesulfonate propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate or mandelate.

[0041] Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide or potassium carbonate.

[0042] Taxol, also referred to as "Paclitaxel", is a well-known anti-cancer drug which acts by inhibiting microtubule

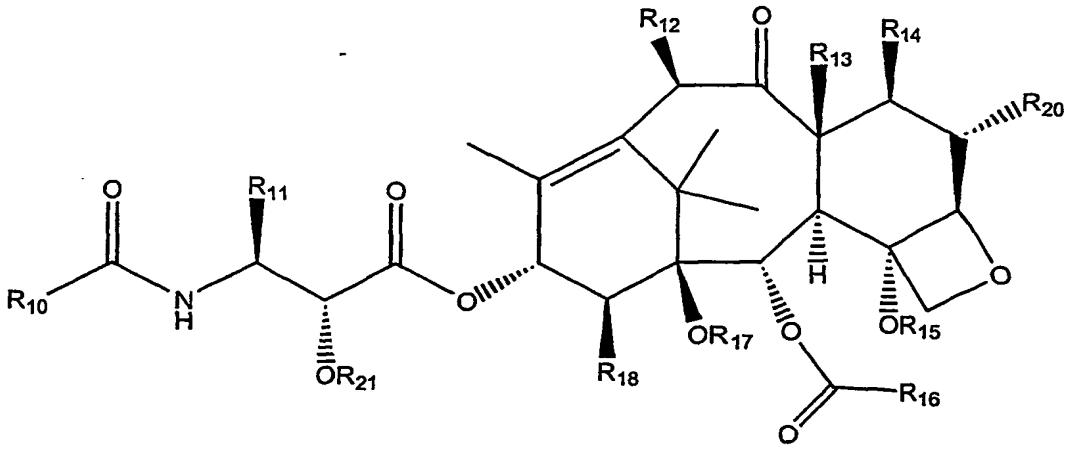
formation. Many analogs of taxol are known, including taxotere, the structure of which is shown in Figure 4. Taxotere is also referred to as ""Docetaxol". The structure of other taxol analogs are shown in Figures 5-25. These compounds have the basic taxane skeleton as a common structure feature and have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules. Thus, it is apparent from Figures 5-25 that a wide variety of substituents can decorate the taxane skeleton without adversely affecting biological activity. It is also apparent that zero, one or both of the cyclohexane rings of a taxol analog can have a double bond at the indicated positions. For clarity purposes, the basic taxane skelton is shown below in Structural Formula (VII):



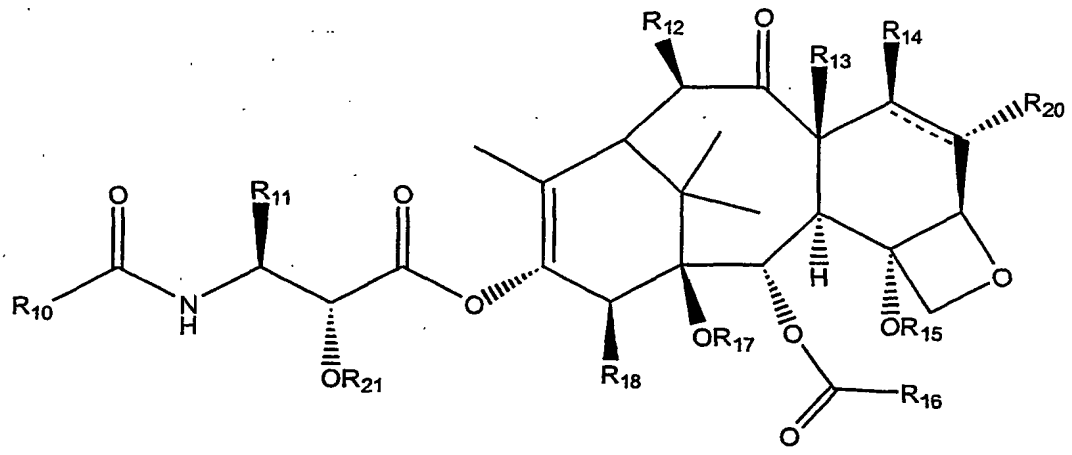
(VII).

Double bonds have been omitted from the cyclohexane rings in the taxane skeleton represented by Structural Formula (VII). It is to be understood that the basic taxane skeleton can include zero or one double bond in one or both cyclohexane rings, as indicated in Figures 5-25 and Structural Formulas (VIII) and (IX) below. A number of atoms have also omitted from Structural Formula (VII) to indicate sites in which structural variation commonly occurs among taxol analogs. For example, substitution on the taxane skeleton with simply an oxygen atom indicates that hydroxyl, acyl, alkoxy or other oxygen bearing substituent is commonly found at the site. It is to be understood that these and other substitutions on the taxane skeleton can also be made without losing the ability to enhance and stabilize microtubule formation. Thus, the term "taxol analog" is defined herein to mean a compound which has the basic taxol skeleton and which promotes disassembly of microtubules.

[0043] Typically, the taxol analogs used herein are represented by Structural Formula (VIII) or (IX):



(VIII).



(IX).

[0044] R_{10} is a lower alkyl group, a substituted lower alkyl group, a phenyl group, a substituted phenyl group, $-SR_{19}$, $-NHR_{19}$ or $-OR_{19}$.

[0045] R_{11} is a lower alkyl group, a substituted lower alkyl group, an aryl group or a substituted aryl group.

[0046] R_{12} is -H, -OH, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, -O-C(O)-(lower alkyl), -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-$(lower alkyl) $-S-CH_2-O-$(lower alkyl).

[0047] R_{13} is -H, $-CH_3$, or, taken together with R_{14}, $-CH_2-$.

[0048] R_{14} is -H, -OH, lower alkoxy, -O-C(O)-(lower alkyl), substituted lower alkoxy, -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-P(O)(OH)_2$, $-O-CH_2-O-$(lower alkyl), $-O-CH_2-S-$(lower alkyl) or, taken together with R_{20}, a double bond.

[0049] R_{15} -H, lower acyl, lower alkyl, substituted lower alkyl, alkoxymethyl, alkthiomethyl, -OC(O)-O(lower alkyl), -OC(O)-O(substituted lower alkyl), - OC(O)-NH(lower alkyl) or -OC(O)-NH(substituted lower alkyl).

[0050] R_{16} is phenyl or substituted phenyl.

[0051] R_{17} is -H, lower acyl, substituted lower acyl, lower alkyl, substituted, lower alkyl, (lower alkoxy)methyl or (lower alkyl)thiomethyl.

[0052] R_{18} -H, $-CH_3$ or, taken together with R_{17} and the carbon atoms to which R_{17} and R_{18} are bonded, a five or six membered a non-aromatic heterocyclic ring.

[0053] R_{19} is a lower alkyl group, a substituted lower alkyl group, a phenyl group, a substituted phenyl group.

[0054] R_{20} is -H or a halogen. ,

[0055] R_{21} is -H, lower alkyl, substituted lower alkyl, lower acyl or substituted lower acyl.

[0056] Preferably, the variables in Structural Formulas (VIII) and (IX) are defined as follows: R_{10} is phenyl, *tert*-butoxy, $-S-CH_2-CH-(CH_3)_2$, $-S-CH(CH_3)_3$, $-S-(CH_2)_3CH_3$, $-O-CH(CH_3)_3$, $-NH-CH(CH_3)_3$, $-CH=C(CH_3)_2$ or *para*-chlorophenyl; R_1 is phenyl, $(CH_3)_2CHCH_2-$, -2-furanyl, cyclopropyl or para-toluyl; R_{12} is -H, - OH, CH_3CO- or $-(CH_2)_2-$*N*-morpholino; R_{13} is methyl, or, R_{13} and R_{14}, taken together, are $-CH_2-$;

[0057] R_{14} is -H, $-CH_2SCH_3$ or $-CH_2-O-P(O)(OH)_2$; R_{15} is CH_3CO-;

[0058] R_{16} is phenyl; R_{17} -H, or, R_{17} and R_{18}, taken together, are -O-CO-O-;

[0059] R_{18} is -H; R_{20} is -H or -F; and R_{21} is -H, $-C(O)-CHBr-(CH_2)_{13}-CH_3$ or $-C(O)-(CH_2)_{14}-CH_3$; $-C(O)-CH_2-CH(OH)-COOH$, $-C(O)-CH_2-O-C(O)-CH_2CH(NH_2)-CONH_2$, $-C(O)-CH_2-O-CH_2CH_2OCH_3$ or $-C(O)-O-C(O)-CH_2CH_3$.

[0060] A taxol analog can also be bonded to or be pendent from a pharmaceutically acceptable polymer, such as a polyacrylamide. One example of a polymer of this type is shown in Figure 26. The term "taxol analog", as it is used herein, includes such polymers.

[0061] The disclosed compounds are enhancers of the anti-cancer activity of taxol and taxol analogs. A compound enhances the anti-cancer activity of taxol or a taxol analog when the activity of taxol or the taxol analog is greater when administered in combination with the compound than when administered alone. The degree of the increase in activity depends upon the amount of compound administered. The compounds of the present invention can therefore be used in combination with taxol or taxol analogs to treat subjects with cancers. Examples include colon cancer, pancreatic cancer, melanoma, renal cancer, sarcoma, breast cancer, ovarian cancer, lung cancer. stomach cancer, bladder cancer and cervical cancer.

[0062] A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs or cats), farm animals (e.g., cows, sheep, pigs or horses) and laboratory animals (e.g., rats, mice or guinea pigs).

[0063] In order to achieve an enhancement of the anti-cancer activity of taxol and taxol analogs, an effective amount of a compound of the present invention and an effective amount of taxol or analog of taxol are administered to the subject. With respect to taxol or an analog of taxol, an "effective amount" is a quantity in which anti-cancer effects are normally achieved. With respect to a compound of the present invention, an "effective amount" is the quantity in which a greater anti-cancer effect is achieved when the compound is co-administered with taxol or a taxol analog compared with when taxol or the taxol analog is administered alone. The compound and taxol (or taxol analog) can be co-administered to the subject as part of the same pharmaceutical composition or, alternatively, as separate pharmaceutical compositions. When administered as separate pharmaceutical compositions, the compound or the present invention and taxol (or taxol analog) can be administered simultaneously or at different times, provided that the enhancing effect of the compound is retained.

[0064] The amount of compound and taxol (or taxol analog) administered to the subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of cancer. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective dosages for taxol and taxol analog are well known and typically range from between about 1 mg/mm^2 per day and about 1000 mg/mm^2 per day, preferably between about 10 mg/mm^2 per day and about 500 mg/mm^2 per day. Effective amounts of a compound of the present invention typically range between about 1 mg/mm^2 per day and about 10 grams/mm^2 per day, and preferably between 10 mg/mm^2 per day and about 5 grams/mm^2.

[0065] The disclosed compounds are administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compounds can also be administered orally (e.g., dietary), topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the type of cancer to be treated. Oral or parenteral administration are preferred modes of administration. Suitable routes of administration of taxol and taxol analogs are well known in the art and include by parenteral administration, as described above for the compounds of the present invention. Suitable routes of administration for taxol and analogs thereof are well known and include *inter alia* parenteral and oral administration.

[0066] The disclosed compounds can be administered to the subject in conjunction with an acceptable pharmaceutical carrier as part of a pharmaceutical composition for treatment of cancer. Formulation of the compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextrasn) are known in the art (Baker, *et al.,* "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).Suitable formulations for taxol and taxol analogs are well known in the art.

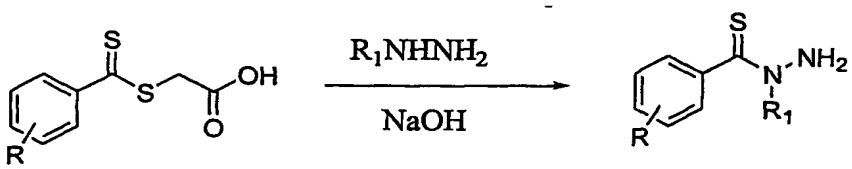
[0067] The disclosed compounds can be prepared according to methods described in Examples 1-12 and also according to methods described in the co-pending US Provisional Application entitled SYNTHESIS OF TAXOL ENHANCERS U.S. Provisional Application No. 60/304,318, filed July 10, 2001. The entire teachings of this application are incorporated herein by reference.

[0068] The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1

[0069]



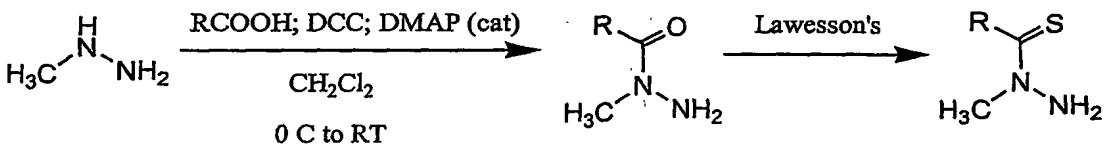
[0070] Preparation of Thiobenzoic acid N-methylhydrazide: Thiobenzoic acid N-methylhydrazide were prepared in 88% yield by slight modification of the prior art (Acta Chem. Scand. 1961, 1087-1096); ^{1}H NMR ($CDCl_3$) δ 3.3 (s, 3H), 6.0 (s, 2H), 7.3-7.4 (m, 5H); ESMS calcd ($C_8H_{10}N_2S$): 166.1; found: 167.1 $(M+H)^+$.

Example 2

[0071] Preparation of Thiobenzoic acid N-methylhydrazide: Bromobenzene (1.6g, 10 mmol) was added into 25 ml anhydrous THF solution containing magnesium powder (0.3g, 12.5 mmol), and refluxed for 2 hr. After it was cooled, the clear reaction solution was added into carbon disulfide (1 ml, 16.8 mmol) at 0 °C, and stirred for 30 min at rt. The resulting mixture was then added into methylhydrazine (1.6 ml, 30mmol) at 0 °C, and stirred for another 2 hours. To this solution was added water (15 ml) and extracted with EtOAc (30 ml x 3). The organic solution was concentrated to minimum volume, and subjected to silica gel column chromatography (eluant: 1:3 -1:1 ethyl acetate : hexanes) to give thiobenzoic acid N^1-methyl hydrazide (0.72 g, total yield: 48 %). ^{1}H NMR ($CDCl_3$) δ 3.3 (s, 3H), 6.0 (s, 2H), 7.3-7.4 (m, 5H); ESMS calcd ($C_8H_{10}N_2S$): 166.1; found: 167.1 $(M+H)^+$.

Example 3

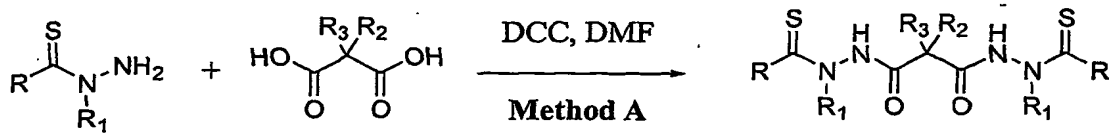
[0072]



[0073] Preparation of 2,5-Dimethoxythiobenzoic acid N-methylhydrazine: DCC (4.5g, 21.8 mmol) was added in one portion to a solution of 2,5-dimethoxybenzoic acid (3.6g, 20 mol), methylhydrazine (1.2 ml, 23 mmol) and DMAP (30 mg, cat.) in CH_2Cl_2 (60 ml) cooled in an ice bath. The reaction mixture was stirred overnight at room temperature. The slurry was cooled at -20 °C for 1 h and filtered. The CH_2Cl_2 solution was evaporated and the residue was dried in vacuum. The resulting crude product was dissolved in toluene (50 ml). To this solution was added Lawesson's reagent (5.8 g, 14 mmol). The mixture was refluxed for 40 min, cooled to room temperature, and directly subjected to silica gel column chromatography (eluent: 25 % to 35 % ethyl acetate in hexanes) to give the 2,5-dimethoxythiobenzoic acid N-methyl-hydrazide (3.7 g, yield: 82%) as off-white solid.^{1}H NMR (300MHz, $CDCl_3$): δ 6.88-6.80(m, 3H), 5.46 (s, 2H), 3.84(s, 3H), 3.82 (s, 3H), 3.28(s, 3H).

Example 4

[0074]

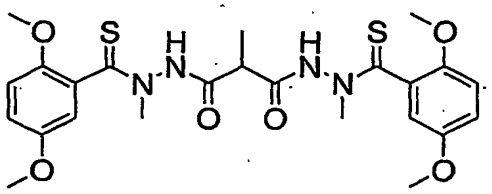


[0075] Preparation of N-Malonyl-bis[N'-methyl-N'-(thiobenzoyl)hydrazide]: To a stirred solution of thiobenzoic acid N-methylhydrazide (0.166 g, 10 mmol), HOBtH_2O (0.15 g, 11 mmol) and malonic acid (0.052 g, 5 mmol) in DMF (2 mL) was added DCC (0.22 g, 10.7 mmol) at 0 °C. The resultant suspension was stirred at 0 °C for 1 h and at room temperature for 3 h. Precipitated material was filtered off and washed with EtOAc (3 x 15 mL). Combined filtrate and washings was washed successively with H_2O (2 x 20 mL), 5% citric acid (20 mL), H_2O (20 mL), Saturated $NaHCO_3$ (20 mL) and brine (20 mL). After being dried over Na_2SO_4, the solvent was removed under reduced pressure to afford the crude product as a yellow solid, which was washed with warm EtOAc. 0.16 g (yield 80%) of pure product was obtained as a yellow powder. R_f 0.3 (Hexane/EtOAc 1:1 v/v); ^{1}H NMR ($CDCl_3$) δ 3.1- 3.8 (m, 6H), 3.4 (s, 2H), 7.1- 7.45 (m, 10 H), 9.5 -10.5

(m, 1H) ppm; ESMS calcd ($C_{19}H_{20}N_4O_2S_2$): 400.1; found: 399.1 $(M-H)^+$.

Preparation of N-(2-Methylmalonyl-bis{N'-methyl-N'-[(2,5-dimethoxy)thiobenzoyl]hydrazide]:

[0076]



[0077] DCC (4 g,19 mmol) was added to a solution of 2,5-dimethoxythiobenzoic acid N-methylhydrazide (3.7 g, 16.4 mmol) and 2-methylmalonic acid (2 g, 17 mmol) in DMF (20 ml) with stirring at 0°C. The reaction mixture was stirred for 1h at room temperature. The slurry was cooled at -20°C for 1 h and filtered. The filtrate was diluted with EtOAc (300 ml), washed with water (50 ml x 3), dried with Na_2SO_4. The EtOAc solution was concentrated to minimum volume, and subjected to silica gel column chromatography (eluent: 1:4 to 2:1, ethyl acetate: hexanes) to give the title compound (3.5 g, 80 %) as yellow powder. ^1H NMR ($CDCl_3$) δ 10.12-9.14 (2H), 7.12-6.81 (m, 6H), 4.01-3.78(m, 6H), 3.75-3.22(m, 6H), 2.82-2.62(m, 1H), 1.12-0.11(m,3H); ESMS cacld ($C_{24}H_{30}N_4O_6S_2$):534.16; found: 535.1 (M+H).

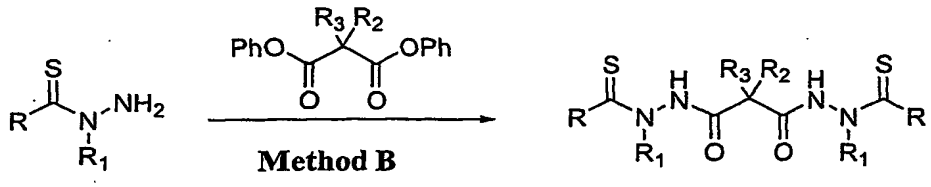
Example 5

[0078]

[0079] Preparation of N-Malonyl-bis[N'-methyl-N'-(thiobenzoyl)hydrazide]: To a solution of thiobenzoic acid N-methylhydrazine (10g) stirred at 0 C were added subsequently triethylamine (8.5 mL) and malonyl dichloride (3.05 mL). The reaction mixture was stirred for 10 min, washed with water (3x50 mL), dried over sodium sulfate and concentrated. Purification by recrystallization from methylene dichloride (35 mL) gave the product as light yellow crystals (9.0 g, 75%) which was identical to the product obtained in Example 6.

Example 6

[0080]

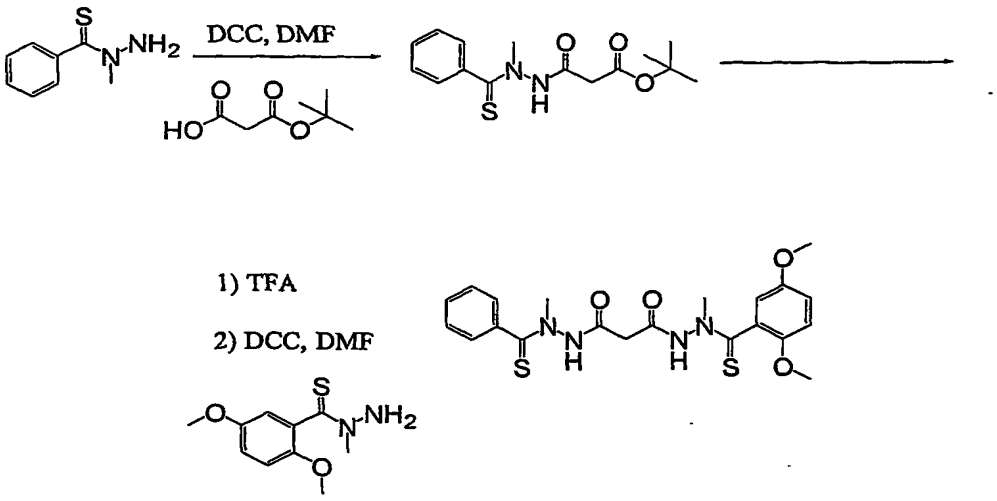


[0081] Preparation of N-Malonyl-bis[N'-methyl-N'-(thiobenzoyl)hydrazide]: A stirred solution of thiobenzoic acid N-methylhydrazide (1.66 g, 10 mmol) and diphenyl malonate (1.30 g, 5.08 mmol) in dry THF (100 mL) was heated to reflux for 72 h. Volatile components were then removed under reduced pressure. The crude product was purified by column

chromatography on silica gel using a mixture of hexane and EtOAc as eluant (gradient from 4:1 v/v to 1: 1 v/v). 1.07 g (51% yield) of pure product N-malonyl-bis[N'-methyl-N'-(thiobenzoyl)hydrazide] was obtained as a yellow powder. Physical property was identical to that obtained in Example 5.

Example 7

[0082]

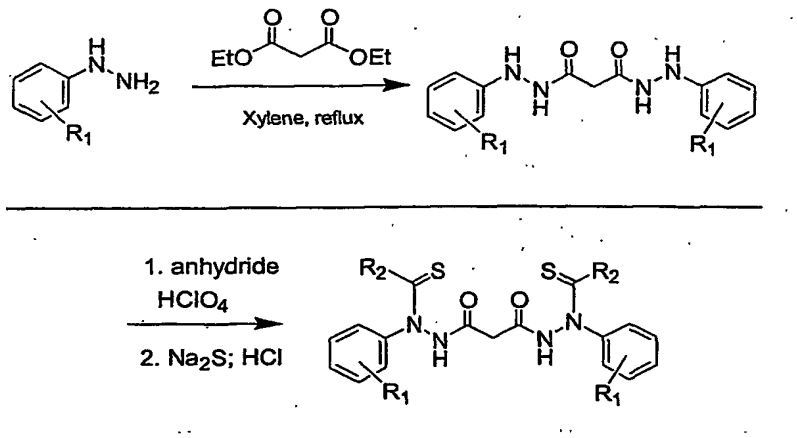


[0083] A slurry of thiobenzoic acid N-methylhydrazide (1.0 g, 6 mmol), mono-tert-butyl malonate (1.0 mL, 6 mmol), HOBt.H_2O (0.98 g, 7.2 mmol), and DCC (1.34 g, 6.5 mmol) in DMF (5 mL) was stirred at 0 °C for 3 h and then at room temperature for 3h. Precipitated material was filtered off and washed with EtOAc (3 x 20 mL). Combined filtrate and washings was washed successively with H_2O (2 x 20 mL), 5% citric acid (20 mL), H_2O (20 mL), Saturated $NaHCO_3$ (20 mL) and brine (20 mL). After being dried over Na_2SO_4, the solvent was removed under reduced pressure to afford the crude product as a solid, which was washed with Et_2O. 0.94 g (yield 51 %) of pure productN'-Methyl-N'-thiobenzoyl-hydrazinocarbonyl)-acetic acid *tert*-butyl ester was obtained as a yellow powder. ^1H NMR ($CDCl_3$) δ 1.6-1.7 (ds, 9H), 3.1-4.1 (m, 5 H), 7.3-7.7 (m, 5H), 9.7-10.3 (ds, 1H)ppm; ESMS calcd ($C_{15}H_{20}N_2O_3S$): 308; found: 307 $(M-H)^+$.

[0084] A solution of N'-methyl-N'-thiobenzoyl-hydrazinocarbonyl)-acetic acid *tert*-butyl ester (0.19g, 0.6 mmol) and TFA (0.12 mL, 1.6 mmol) in dry DCM (10 mL) was stirred at 10 °C -15 °C for 12 h (reaction was monitored by TLC). Volatile components were removed under reduced pressure (bath temperature below 5°C). After being dried in vacuo, DMF (3 mL) was added followed by the addition of DCC (0.13 g, 0.6 mmol), HOBtH_2O (93 mg, 0.7 mmol) and thio-2,5-dimethoxybenzoic acid N-methylhydrazide (0.13 g, 0.57 mmol). The resultant solution was stirred at 0 °C for half an hour and then at room temperature for 3h. Precipitated material was filtered off and washed with EtOAc (3 x 10 mL). Combined filtrate and washings was washed successively with H_2O (2 x 10 mL), 5% citric acid (10 mL), H_2O (10 mL), Saturated $NaHCO_3$ (20 mL) and brine (20 mL). After being dried over Na_2SO_4, the solvent was removed under reduced pressure to afford the crude product as an oil, which was purified by SGC (4:1 hexane/EA to 2:1 EtOAc/Hexane). 0.14 g (yield 53%) of pure product was obtained as a yellow powder. ^1H NMR ($CDCl_3$) δ 3.1-3.9 (m,18H), 6.7-7.4 (m, 9H) ppm; ESMS calcd ($C_{21}H_{24}N_4O_4S2$): 460.1; found: 461.1 $(M+H)^+$.

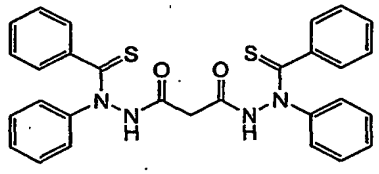
Examples 8

[0085]



Preparation of N- N-malonyl-bis[N'-phenyl-N'-(thiobenzoyl)hydrazide]

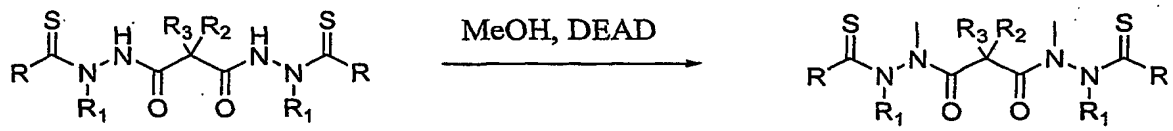
[0086]



[0087] A mixture of phenylhydrazine (30 mL) and ethyl malonate (in xylene (150 mL) was heated to reflux overnight. The reaction was cooled to room temperature. The precipitates were collected via filtration and washed with ethanol to give N-malonyl-bis(N'-phenylhydrazide) as a white solid (14 g). The hydrazide (3.4 g) was suspended in benzoic anhydride (50 g) with warming. To it was added dropwise perchloric acid (57% in water, 3 mL). The reaction mixture turned to clear solution initially and then quickly solidified. After standing at room temperature for 1 h, ether (50 mL) was added. The resulting slurry was filtered and washed with ether (2 x 00 mL) to give the perchlorate salts as a white solid (5.7 g). The salts were taken into acetone and added as a slurry over 5 min to Na_2S (0.6 M in water, 90 mL) stirred at room temperature. After 30 min, the reaction was acidified with HCl(c) to afford a yellow slurry. The solid was collected via filtration and washed with water (20 mL) and ether (2x25 mL) to give N-malonyl-bis[N'-phenyl-N'-(thiobenzoyl)hydrazide] as an off-white solid (3.6 g). ^1H NMR ($CDCl_3$): δ 7.2 (m, 20H); 3.5 (br s, 2H). MS calcd for $C_{29}H_{24}N_4O_2S_2$: 524.13: Found: 525.1 (M+H).

Example 9

[0088]



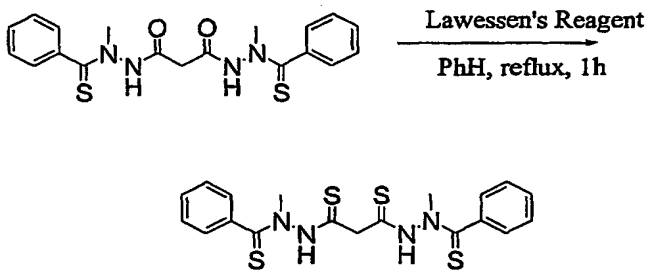
Preparation of N-Malonyl-bis[N-methyl-N'-phenyl-N'-(thiobenzoyl)hydrazide]

[0089] To a stirred solution of N-malonyl-bis[N'-phenyl-N'-(thiobenzoyl)hydrazide] (180 mg, 0.34 mmol), MeOH (22 uL) and triphenylphosphine (200 mg, 0.64 mmol) in dry THF(10 mL) was added a solution of DEAD (0.12 mL) in THF (3 mL) dropwise. The resultant orange solution was stirred at room temperature for 12 h. After removal of the volatile

components, the crude product was purified by SGC (3:1 Hexane/EtOAc) to afford 98 mg (52% yield) of the title compound as syrup. ^{1}H NMR ($CDCl_3$) δ 3.3-4.5 (m, 8H), 7.1-7.8 (m, 20 H)ppm; ESMS calcd ($C_{31}H_{28}N_4O_2S_2$): 552; found: 551 $(M-H)^+$.

Example 10

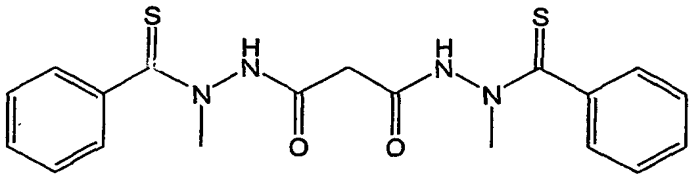
[0090]



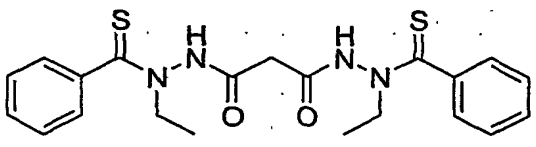
[0091] A stirred mixture of N-malonyl-bis[N'-phenyl-N'-(thioacetyl)hydrazide) starting material (0.1 g, 0.25 mmol) and Lawesson's reagent (0.15 g, 0.37 mmol) in dry benzene (20 mL) was heated to reflux for 1 h. After being cooled to room temperature, the mixture was filtered through a layer of silica gel, washed with THF (2 x 15 mL). The filtrate and washings were combined and concentrated under reduced pressure. Flush column chromatography on silica gel (hexane to 4:1 hexane/EtOAc to 2:1 hexane/EtOAc) afforded N-bisthiomalonyl-bis[N'-phenyl-N'-(thioacetyl)hydrazide as a clear syrup (16 mg, 15%). ^{1}H NMR ($CDCl_3$) δ 3.80-3.95 (m, 8H), 7.02-7.30 9m, 10 H). ESMS calcd ($C_{19}H_{20}N_4S_4$): 432.06; found: 433.0 $(M+H)^+$.

Example 11

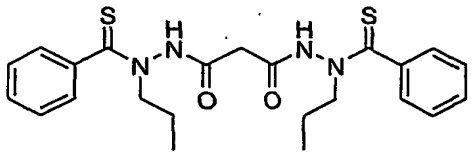
[0092] The compounds shown below were prepared by the procedures described above. Analytical data is provided for these compounds.



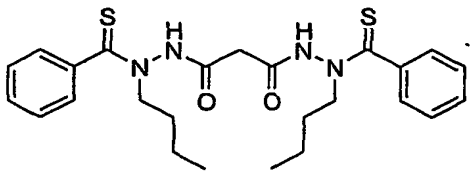
^{1}H NMR ($CDCl_3$) δ 3.1- 3.8 (m, 6H), 3.4 (s, 2H), 7.1-7.45 (m, 10 H), 9.5 - 10.5 (m, 1H) ppm; ESMS calcd ($C_{19}H_{20}N_4O_2S_2$): 400.1; found: 399.1 $(M-H)^+$.



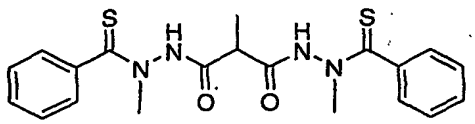
^{1}HNMR ($CDCl_3$) δ 1.0-1.35 (m, 6H), 3.0-4.3 (m, 6H), 7.05-7.40 (m, 10H), 9.1-10.1 (m, 2H); ESMS cacld ($C_{21}H_{24}N_4O_2S_2$): 428.8; found: 427 $(M-H)^+$. Anal Calc For $C_{21}H_{24}N_4O_2S_2$ (428.13) C, 58.85; H, 5.64; N, 13.07; S, 14.96. Found: C, 58.73; H, 5.62; N, 12.97; S, 14.96.



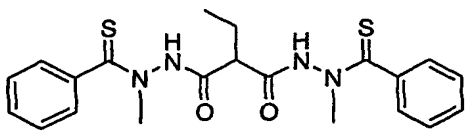
^{1}H NMR ($CDCl_3$) δ 0.7-1.0 (m, 6H), 1.4-1.9 (m, 4H), 3.1-4.2 (m, 6H), 7.1-7.4 (m, 10H), 8.9-10.2 (m, 2H) ppm; ESMS ($C_{23}H_{28}N_4O_2S_2$): 456.1; found: 455.1 $(M-H)^+$.



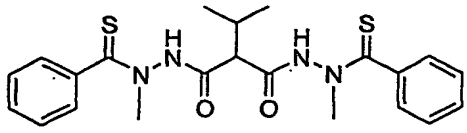
mp 141-143°C;^{1}H NMR ($CDCl_3$) 8 0.6-1.05 (m, 6H), 1.1-1.9 (m, 8H), 3.0-4.2 (m, 6H), 7.0-7.35 (m, 10H), 8.9-11 (ms, 2H). ESMS ($C_{25}H_{32}N_4O_2S_2$): 484.2; found: 483.1 $(M-H)^+$. Anal Calc For $C_{25}H_{32}N_4O_2S_2$ (484.2) C, 61.95; H; 6.65; N, 11.56; S, 13.23. Found: C, 61.98; H, 6.52; N, 11.26; S, 13.16.



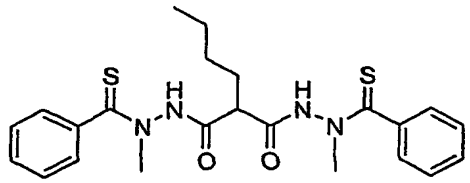
^{1}H NMR (DMSO-d_6) δ 0.4-0.9 (dd, 3H, J = 7), 2.7 (q, 1H), 3.1- 3.6 (m, 6H), 7.1- 7.5 (m, 10H), 10.9 (br, 2H)ppm; ESMS ($C_{20}H_{22}N_4O_2S_2$): 414; found: 413 $(M-H)^+$.



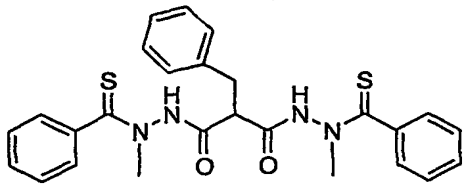
^{1}H NMR ($CDCl_3$) δ 0.5 (t, 3H, J = 7), 1.1-1.6 (m, 2H), 2.7 (t, 1H, J = 7), 3.1- 3.3 (m, 6H), 7.0-7.3 (m, 10H), 10.25 (s, 2H) ppm; MS ($C_{21}H_{24}N_4O_2S_2$): 428.1; found: 427.1 $(M-H)^+$.



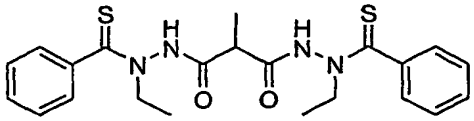
^{1}H NMR ($CDCl_3$) δ 0.5 (d, 6H, J =7), 0.9-1.2 (m, 1H), 3.0-41 (m, 7H), 7.1-7.4(m, 10H), 10.3 (s, 2H)ppm; ESMS ($C_{22}H_{26}N_4O_2S_2$): 442.1; found: 441.1 $(M-H)^+$.



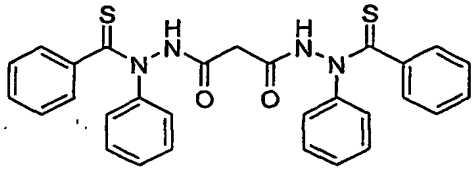
^{1}H NMR ($CDCl_3$) δ 0.4-1.3 (m, 5H), 1.5-1.8 (m, 2H), 3.0-3.7 (m, 6H), 7.1-7.5 (m, 10H), 11 (s, 2H) ppm; ESMS ($C_{23}H_{28}N_4O_2S_2$): 456.1; found: 455.1 $(M-H)^+$.



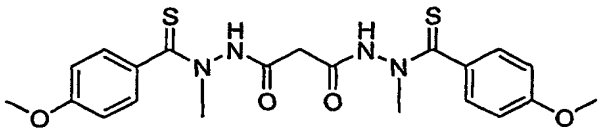
^{1}H NMR ($CDCl_3$) δ 2.1 (d, 2H, J =7), 2.9 (t, 1H, J =7), 3.1-3.5 (m, 6H), 6.8-7.4 (m, 15 H), 11 (s, 2H)ppm; ESMS ($C_{26}H_{26}N_4O_2S_2$): 490.1; found: 489.1 $(M-H)^+$.



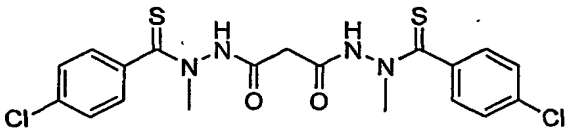
^{1}H NMR ($CDCl_3$) δ 0.4 (d, 3H, J = 7), 1.0-1.4 (m, 6H), 2.75 (q, 1H), 3.0-4.3 (m, 4H), 7.1-7.4 (m, 10H), 10.6 (s, 2H); ESMS Calc For ($C_{22}H_{26}N_4O_2S_2$): 442.1; found: 441.1 $(M-H)^+$; Anal Calc For $C_{22}H_{26}N_4O_2S_2$ (442.15) C, 59.70; H, 5.92; N, 12.66; S, 14.49. Found: C, 59.64; H, 5.92; N, 12.59; S, 14.47.



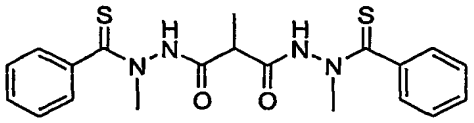
^{1}H NMR (DMSO-d_6) δ 3.20 (br, 2H), 7.1-7.6 (m, 20 H), 11.5 (s, 2H) ppm; ESMS calcd ($C_{29}H_{24}N_4O_2S_2$): 524.1; found: 523.1 $(M-H)^+$.



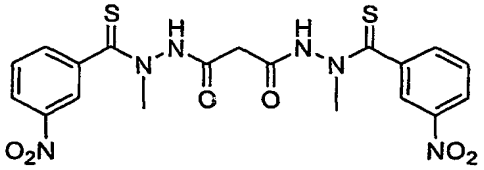
^{1}H NMR ($CDCl_3$) δ 3.0-4.3 (m, 14H), 6.6-7.5 (m, 8H), 10.4 (s, 2H) ppm; ESMS calcd ($C_{21}H_{24}N_4O_2S_2$): 460.2; found: 461.2 $(M+H)^+$.



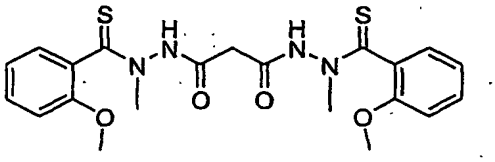
^{1}H NMR ($CDCl_3$) δ 2.65-3.60 (m, 8H), 7.2-7.4 (m, 8H), 11.1 (br, 2H); ESMS calcd ($C_{19}H_{18}Cl_{12}N_4O_2S_2$): 468.0; found: 467.9 $(M-H)^+$.



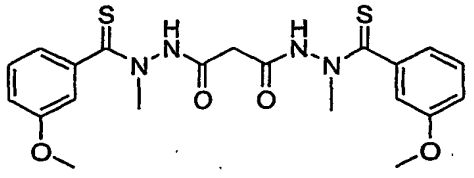
^{1}H NMR ($CDCl_3$) δ 0.4 (d, 3H, J = 7), 2.7 (q, 1H, J = 7), 3.0-3.8 (m, 6H), 7.2-8.2 (m, 8H), 10.5-10.7 (ms, 2H) ppm; ESMS calcd ($C_{20}H_{20}Cl_2N_4O_2S_2$): 482.0; found: 481.0 $(M-H)^+$.



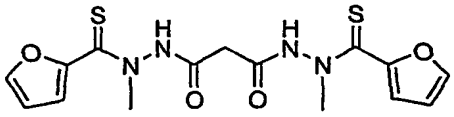
^{1}HNMR ($CDCl_3$) δ 2.9-3.8 (m, 6H), 7.3-7.7 (m, 4H), 8.0-8.3 (m, 4H), 10.9 (s, 2H); ESMS calcd ($C_{10}H_{18}N_6O_6S_2$): 490.0; found: 489.0 $(M-H)^+$.



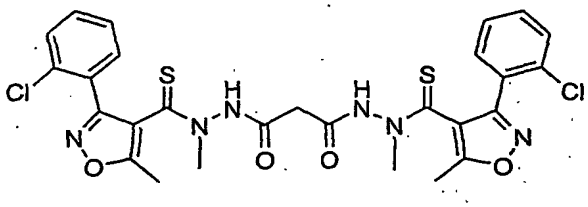
^{1}H NMR ($CDCl_3$) δ 3.1-3.9 (m, 14H), 6.7-7.8 (m, 8H), 9.0-10 (m, 2H) ppm; ESMS calcd ($C_{21}H_{24}N_4O_4S_2$): 460.1; found: 459.1 $(M-H)^+$.



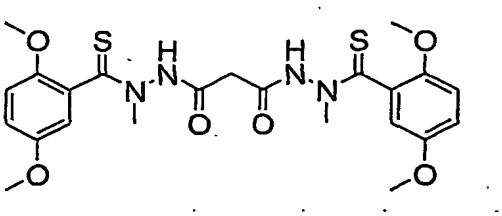
(SBR-11-5032): ^{1}H NMR ($CDCl_3$) δ 3.0-3.9 (m, 14H), 6.7-7.3 (m, 8H), 9.0-10 (m, 2H) ppm; ESMS calcd ($C_{21}H_{24}N_4O_4S_2$): 460.1; found: 459.1 $(M-H)^+$.



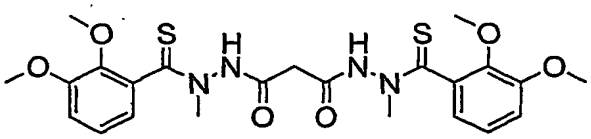
^{1}H NMR (acetone-d_6) δ 3.5 (s, 2H), 6.45 (d, 2H, J = 5), 6.9 (d, 2H, J = 5), 7.2-7.6 (m, 12H), 10.6 (s, 2H) ppm; ESMS calcd ($C_{25}H_{20}N_4O_4S_2$): 504.1; found: 503.1 $(M-H)^+$.



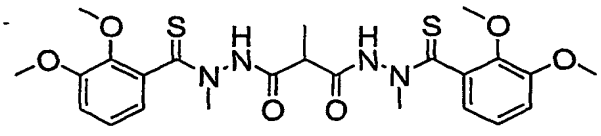
^{1}H NMR (DMSO-d6) δ 2.60 (s, 6H), 3.05 (s, 6H), 3.40 (s, 2H), 7.15-7.50 (m, 8H)ppm; ESMS calcd ($C_{27}H_{24}Cl_2N_6O_4S_2$): 630.1; found: 629.1 $(M-H)^+$.



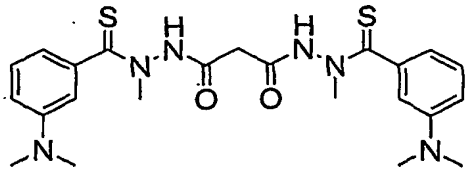
^{1}H NMR ($CDCl_3$) δ 10.06-8.82 (2H), 7.16-6.81(m,6H), 4.01-3.81(m, 6H), 3.78-3.11(m,6H), 2.81-2.58(m,2H): ESMS cacld ($C_{23}H_{28}N_4O_6S_2$): 520.15; found: 521 (M+H).



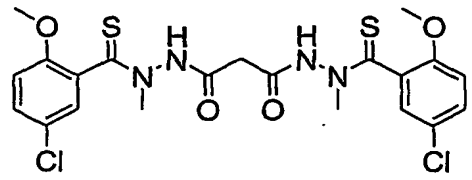
^{1}H NMR ($CDCl_3$) δ 10.38-9.01 (2H), 7.12-6.82 (m, 6H), 3.92-3.78(m, 12H), 3.75-3.06(m, 6H), 2.61-2.51 (m, 2H); ESMS cacld ($C_{23}H_{28}N_4O_6S_2$): 520.15; found: 521 (M+H).



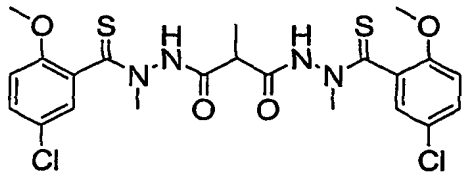
^{1}H NMR ($CDCl_3$) δ 9.45-8.63 (2H), 7.18-6.81 (m, 6H), 4.01-3.80(m, 6H), 3.78-3.24(m, 6H), 2.62-2.50(m, 1H), 1.74-0.11 (m, 3H); ESMS cacld ($C_{24}H_{30}N_4O_6S_2$):534.16; found: 535 (M+H).



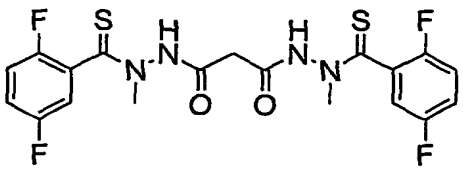
^{1}H NMR ($CDCl_3$) δ 10.19-8.61 (2H), 7.26-6.52(m, 6H), 3.81-3.08(m, 8H), 3.01-2.88(m, 12H). ESMS cacld ($C_{23}H_{30}N_6O_2S_2$): 486.19; found: 487 (M+H).



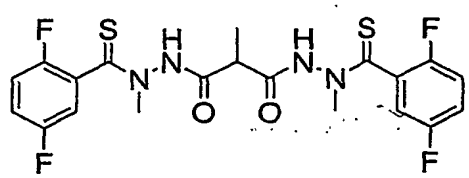
^{1}H NMR ($CDCl_3$) δ 9.92-8.80 (2H), 7.41-6.72 (m, 6H), 4.01-3.81(m,6H), 3.80-3.15 (m,6H), 2.76-2.42(m, 2H); ESMS cacld ($C_{21}H_{22}Cl_2N_4O_4S_2$):528.05; found: 529(M+H).



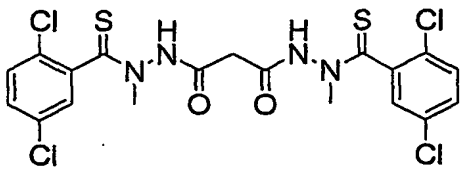
^{1}H NMR ($CDCl_3$) δ 10.21-9.02(2H), 7.60-6.81 (m, 6H), 4.14-3.88(m, 6H), 3.87-3.18 (m,6H), 2.84-2.65(m, 1H),1.10-0.16 (m, 3H); ESMS cacld ($C_{22}H_{24}Cl_2N_4O_4S_2$): 542.06; found: 543(M+H).



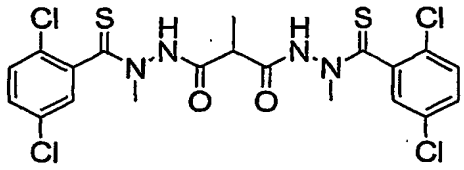
^{1}H NMR ($CDCl_3$) δ 10.02-9.20 (2H), 7.63-7.01 (m, 6H), 4.21-3.22(m, 6H), 1.88-1.36 (m, 2H); ESMS cacld ($C_{19}H_{16}F_4N_4O_2S_2$): 472.07; found: 473 (M+H).



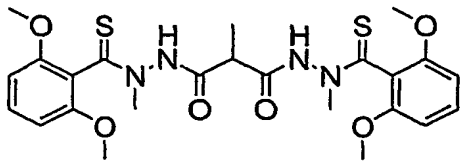
^{1}H NMR ($CDCl_3$) δ7.93-7.61 (2H), 7.40-6.92 (m, 6H), 3.98-3.41 (m, 6H), 2.19-0.93 (m, 4H); ESMS cacld ($C_{20}H_{18}F_4N_4O_2S_2$): 486.08; found: 487 (M+H).



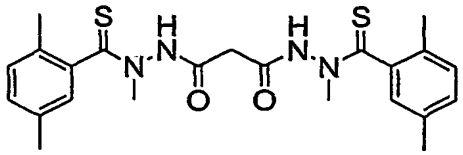
^{1}H NMR ($CDCl_3$) δ 10.12-9.21(2H), 7.67-7.23 (m, 6H), 3.94-3.22 (m, 6H), 2.01-1.21 (m, 2H); ESMS cacld ($C_{19}H_{16}Cl_4N_4O_2S_2$): 535.95; found: 537(M+H).



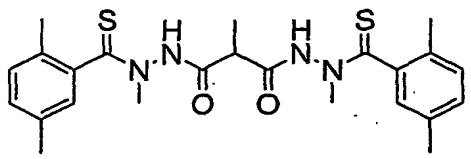
^{1}H NMR ($CDCl_3$) δ 7.78-7.23 (2H), 4.56-3.10 (m, 6H), 2.34-1.12 (m, 4H); ESMS cacld ($C_{20}H_{18}Cl_4N_4O_2S_2$): 549.96; found: 551 (M+H).



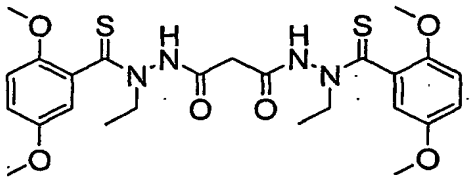
^{1}H NMR ($CDCl_3$) δ 9.92-9.01 (2H), 7.38-7.15 (m,3H), 6.66-6.51 (m,3H), 3.98-3.75 (m,12H), 3.72-3.21(m,6M, 2.01-0.42 (m, 4H); ESMS cacld ($C_{24}H_{30}N_4O_6S_2$):534.16; found: 535 (M+H).



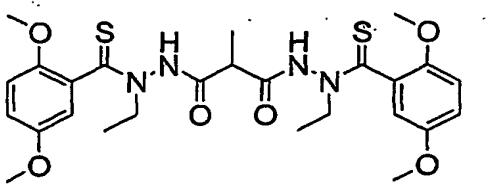
^{1}H NMR ($CDCl_3$) δ 10.51-9.82 (2H), 7.42-6.80 (m, 6H), 3.92-3.04(m, 6H), 2.60-1.21 (m, 14H); ESMS cacld ($C_{23}H_{28}N_4O_2S_2$): 456.17; found: 457(M+H).



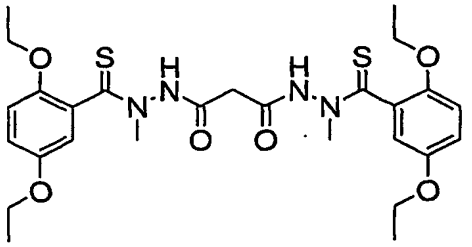
^{1}H NMR ($CDCl_3$) δ 10.51-8.82 (2H), 7.11-6.89 (m, 6H), 3.81-3.02,(m, 6H), 2.40-1.02 (m, 16H); ESMS cacld ($C_{24}H_{30}N_4O_2S_2$): 470.18; found: 471(M+H).



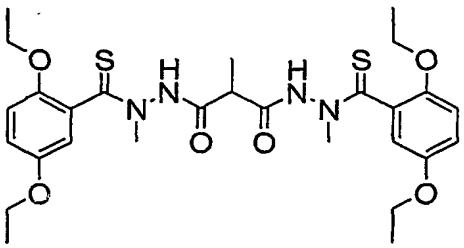
^{1}H NMR ($CDCl_3$) δ 9.86-8.42 (2H), 7.01-6.6 (m, 6H), 4.18-3.51 (m, 16H), 3.22-2.26 (2H), 1.40-1.04 (m, 6H); ESMS cacld ($C_{25}H_{32}N_4O_6S_2$):548.18; found: 547 (M-H).



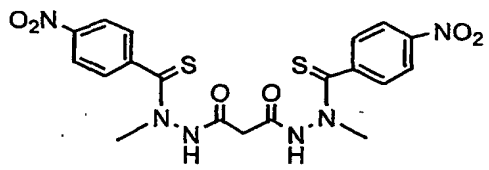
^{1}H NMR ($CDCl_3$) δ 9.99-8.41 (2H), 7.01-6.68 (m, 6H), 4.18-3.56 (m, 16H), 1.40-0.02 (m, 10H); ESMS cacld ($C_{26}H_{34}N_4O_6S_2$): 562.19; found: 561(M-H).



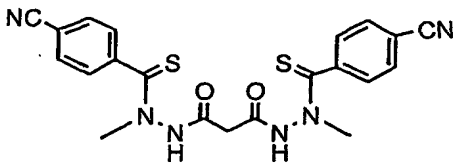
^{1}H NMR ($CDCl_3$) δ 10.12-8.82 (2H), 7.03-6.62 (m, 6H), 4.21-3.87 (m, 8H), 3.84-3.01(m, 6H), 2.71-2.42 (m, 2H), 1.56-1.21 (m, 12H); ESMS cacld ($C_{27}H_{36}N_4O_6S_2$): 576.21; found: 577(M+H).



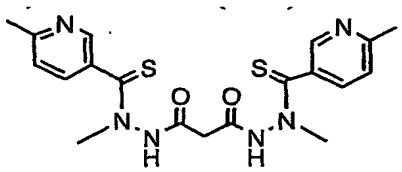
^{1}H NMR ($CDCl_3$) δ 9.81-8.79 (2H), 7.01-6.64 (m, 6H), 4.21-3.81(m, 8H), 3.80-3.22 (m, 6H), 1.54-1.20 (m, 13H), 1.01-0.16 (m, 3H); ESMS cacld ($C_{28}H_{38}N_4O_6S_2$): 590.22; found: 591(M+H).



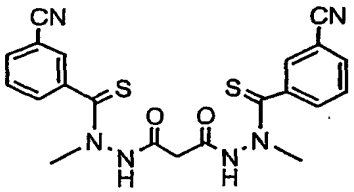
^{1}H NMR (DMSO-d_6): δ 8.25 (d, J=8.1 Hz, 4H), 7.50 (d, J=8.1 Hz, 4H), 3.7-3.3 (m, 8H); ESMS cacld for $C_{19}H_{18}N_6O_6S_2$: 490.1; Found: 489.0 (M-H).



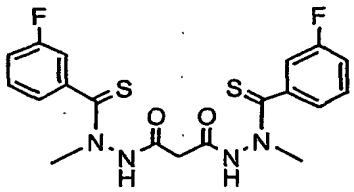
^{1}H NMR ($CDCl_3$): δ 10.25 (m, 2H), 7.7-7.4 (m, 8H), 3.7 (m, 2H), 3.35 (m, 6H); ESMS cacld for $C_{21}H_{18}N_6O_2S_2$: 450.1; Found: 449.0 (M-H).



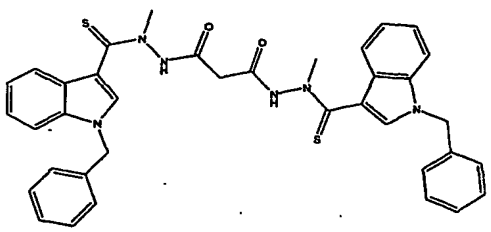
^{1}H NMR ($CDCl_3$): δ 8.2 (s, 2H), 7.7-7.5 (m, 4H), 3.7-3.4 (m, 8H), 2.9-2.8 (m, 6H); ESMS cacld for $C_{19}H_{22}N_6O_2S_2$: 430.1; Found: 431.1 (M+H).



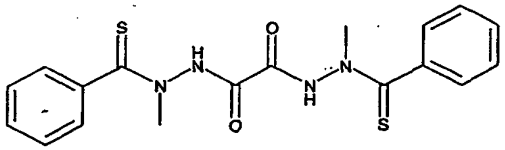
^{1}H NMR ($CDCl_3$): δ 10.0-9.2 (m, 2H), 7.9-7.45 (m, 8H), 4.0-3.4 (m, 8H); ESMS cacld for $C_{21}H_{18}N_6O_2S_2$:450.1; Found: 451.0 (M+H).



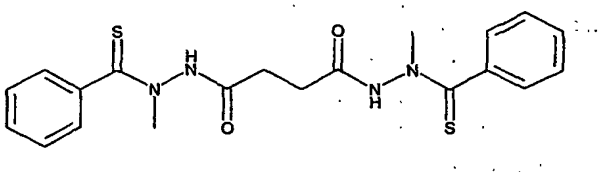
^{1}H NMR ($CDCl_3$): δ 10.1-9.4 (2H), 7.5-7.2 (m, 8H), 3.9-3.3 (m, 8H); ESMS cacld for $C_{19}H_{18}F_2N_4O_2S_2$: 436.1; Found: 437.1 (M+H).



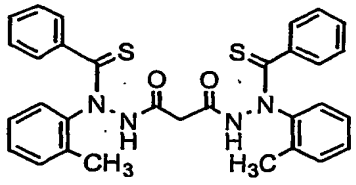
^{1}H NMR ($CDCl_3$): δ 3.3 (s, 2H), 3.6 (s, 6H), 5.25 (s, 4H), 7.05-7.3 (m, 16H), 7.6 (s, 2H), 7.9 (d, 2H, J = 6), 10.56 (s, 2H) ppm; ESMS calcd ($C_{37}H_{34}N_6O_2S_2$): 658.2; found: 659.2 $(M+H)^+$.



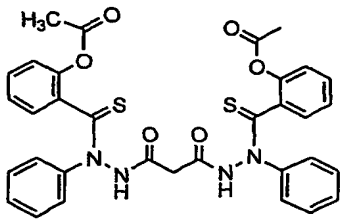
^{1}H NMR (DMSO) δ 11.98 (2H), 7.44-7.12 (m, 10H), 3.69-3.14(s, 6H). ESMS cacld ($C_{18}H_{18}N_4O_2S_2$): 386.09: found: 387.1 (M+H).



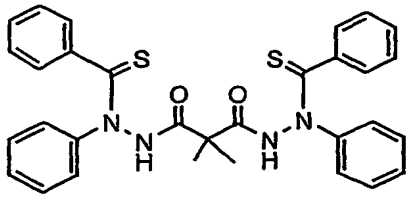
^{1}HNMR ($CHCl_3$) δ 9.48-8.55 (2H), 7.56-7.20(m, 10H), 3.80-3.31(m, 6H), 2.88-2.22(m, 4H). ESMS cacld ($C_{20}H_{22}N_4O_2S_2$): 414.12; found: 415.1 (M+H).



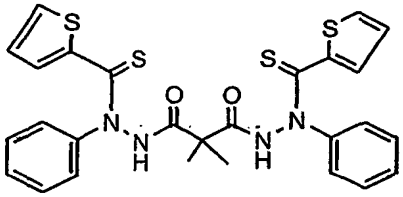
^{1}H NMR ($CDCl_3$): δ 7.2 (m, 18H); 3.5 (br s, 2H); 2.4 (br s, 6H). MS calcd for $C_{31}H_{28}N_4O_2S_2$: 552.2: Found: 553.2 (M+H).



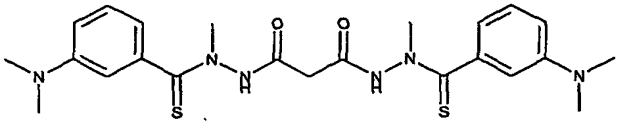
^{1}H NMR ($CDCl_3$): δ 7.5 (br s, 18H), 3.4 (br s, 2H), 2.45 (s, 6H). ESMS cacld for $C_{33}H_{28}N_4O_6S_2$: 640.1; Found 641.1 (M+H).



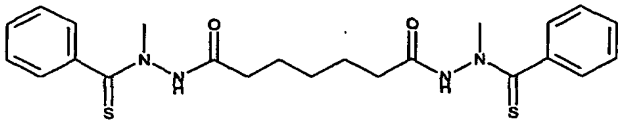
^{1}H NMR ($CDCl_3$-D_2O): δ 7.45-7.15 (m, 20 H), 1.6 (br s, 6H). ESMS cacld for $C_{31}H_{28}N_4O_2S_2$: 552.2; Found: 553.2 (M+H).



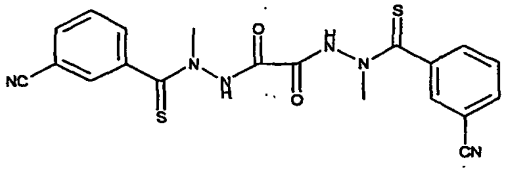
^{1}H NMR (DMSO-d_6): δ 11.3 (s, 2H), 7.75 (d, J=6.0 Hz, 2H), 7.5-7.4 (m, 12 H); 6.9 (m, 2H); ESMS cacld for $C_{27}H_{24}N_4O_2S_4$: 564.1; Found: 565.2 (M+H).



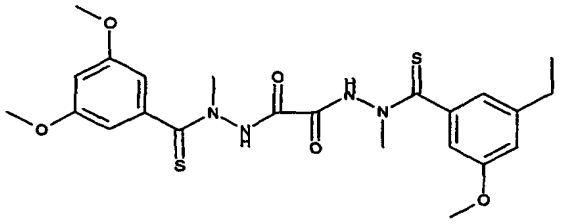
^{1}H NMR (300MHz, $CDCl_3$): δ 10.18-8.60 (m, 2H), 7.26-6.46 (m, 8H), 3.80-3.02(m, 6H), 3.00-2.80(m, 12H). 1.78-1.56 (m, 2H), ESMS cacld($C_{23}H_{30}N_4O_2S_2$):486.19; found: 487 (M+H).



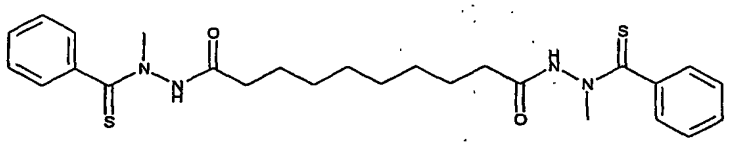
^{1}H NMR (300MHz, DMSO): δ 10.90-10.81 (m, 2H), 7.50-7.21 (m, 10H), 3.78-3.36(m, 6H), 2.64-0.50(m, 10H). ESMS cacld($C_{20}H_{28}N_4O_2S_2$): 456.17; found: 457 (M+H).



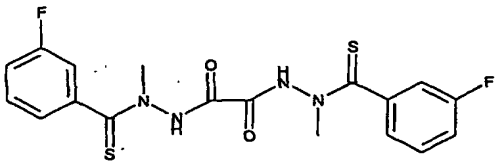
^{1}H NMR (300MHz, $CDCl_3$): δ 10.00-9.71 (m, 2H), 7.72-7.21(m, 8H), 3.80-3.26(m, 6H). ESMS cacld($C_{20}H_{16}N_6O_2S_2$): 436.08; found: 437 (M+H).



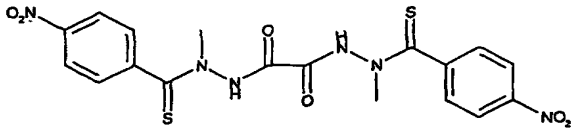
^{1}HNMR (300MHz, $CDCl_3$): δ 10.60-9.41 (m, 2H), 7.15-6.23(m, 6H), 3.89-3.28(m, 6H), 3.76(S, 12H). ESMS cacld ($C_{22}H_{28}N_4O_6S_2$):506.13; found:507 (M+H).



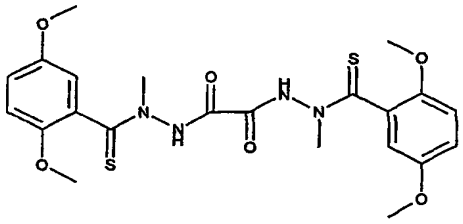
^{1}H NMR (300MHz, DMSO): δ 7.40-7.12 (m, 10H), 3.70-2.80(m, 6H), 1.84-0.72(m, 16H). ESMS cacld($C_{26}H_{34}N_4O_2S_2$): 498.21; found: 499 (M+H).



^{1}H NMR (300MHz, $CDCl_3$): δ 10.42-9.53 (m, 2H), 7.55-6.87(m, 8H), 3.99-3.28(m, 6H), ESMS cacld($C_{18}H_{10}N_4F_2O_2S_2$): 422.07; found: 423 (M+H).

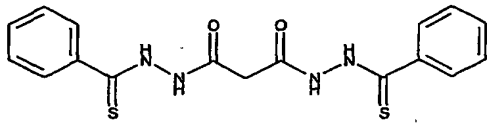


^{1}H NMR (300MHz, DMSO): δ 12.08 (br. 2H), 8.27-7.24 (m, 8H), 3.70-3.15(m, 6H). ESMS cacld($C_{18}H_{16}N_6O_6S_2$):476.06; found: 477 (M+H).

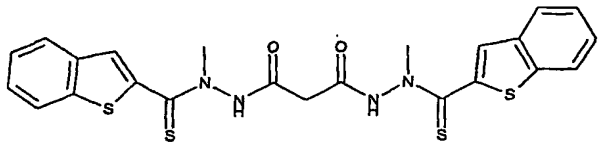


^{1}HNMR (300MHz, $CDCl_3$): δ 10.12-9.83 (m, 2H), 7.15-6.63(m, 6H), 3.99-2.91(m, 6H), ESMS cacld($C_{22}H_{26}N_4O_6S_2$):

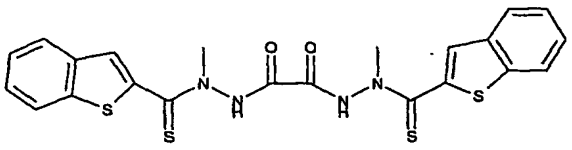
506.13; found: 507 (M+H).



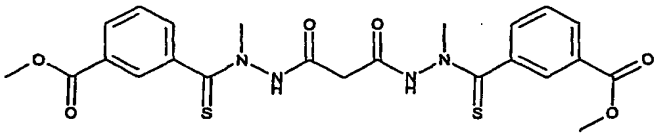
^{1}H NMR (300MHz, DMSO): δ 11.12-10.54 (m, 2H), 8.27-7.18 (m, 10H), 4.26-3.72(m, 2H), 3.37-3.18(m, 2H). ESMS cacld($C_{17}H_{16}N_4O_2S_2$):372.07; found: 371 (M-H).



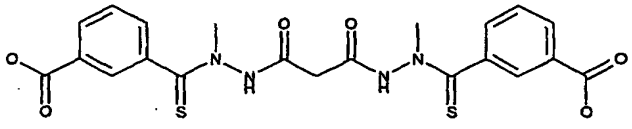
^{1}H NMR (300MHz, DMSO): δ 11.52 (br, 2H), 7.95-7.33(m, 10H), 3,42-3.22(m, 6H), 2.48(m, 2H). ESMS cacld ($C_{23}H_{20}N_4O_2S_4$):512.05; found: 513 (M+H).



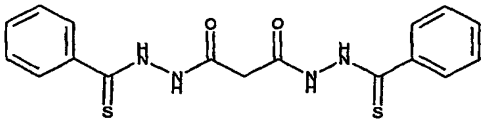
^{1}H NMR (300MHz, $CDCl_3$): δ 7.81-7.28(m, 8H), 3.82(s, 6H). ESMS cacld($C_{22}H_{18}N_4O_2S_4$):498.03; found: 499 (M+H).



^{1}H NMR (300MHz, $CDCl_3$): δ 10.02-9.11 (m, 2H), 8.16-7.28(m, 8H), 3.99-3.08(m, 6H), 2.90-1.20(m, 2H). ESMS cacld ($C_{23}H_{24}N_4O_6S_2$):516.11; found: 517 (M+H).



^{1}H NMR (300MHz, DMSO): δ 7.99 (m, 8H), 8.16-7.28(m, 8H), 3.80-3.14(m, 6H), 1.80-1.21(m, 2H). ESMS cacld ($C_{21}H_{20}N_4O_6S_2$):488.08; found: 487 (M-H).



^{1}H NMR (300MHz, $CDCl_3$): δ 10.82-10.55 (m, 2H), 7.91-7.29(m, 10H), 3.64-3.11 (m, 6H), 1.90-1.40(m, 2H). ESMS cacld ($C_{19}H_{20}N_4O_2S_2$):400.19; found: 399 (M-H).

Example 12 - Compound (1) Enhances the Anti-Cancer Activity of Paclitaxel *In Vivo* General Procedure of *In Vivo* Anti-Tumor Study

[0093] The *in vivo* anti-cancer enhancing effect of novel compounds was assessed in tumor bearing mice using the tumor growth inhibition assay. Tumor cells were implanted by injection of a tumor cell suspension subcutaneously in the flank of a mouse. Treatment of the tumor with an experimental compound and Paclitaxel begun after the tumor had been established (volume was about 100 mm^3). Animal then begun a multiple injection schedule where the compound and Paclitaxel were given by IV route of administration. Tumors were measured two times a week. During the course of this assay, animals were monitored daily for signs of toxicity including body weight loss.

PROCEDURE

[0094] A supplemented media was prepared from 50% DMEM/Dulbecco Modified Eagle Medium (High Glucose), 50% RPMI 1640, 10% FBS/Fetal Bovine Serum (Hybridoma Tested; Sterile Filtered), 1% L-Glutamine, 1% Penicillin-Streptomycin, 1% MEM Sodium Pyruvate and 1% MEM Non-Essential Amino Acids. FBS was obtained from Sigma Chemical Co. and other ingredients were obtained from Invitrogen Life Technologies, USA). The supplemental media was warmed to 37 °C and 50 ml of media was added to a 175 cm^2 tissue culture flask.

[0095] The cells used in the assay were MDA-435 Human Breast Carcinoma from the American Type Culture Collection. 1 vial of MDA-435 cells from the liquid nitrogen frozen cell stock was removed. The frozen vial of cells was immediately placed into a 37 °C water bath and gently swirled until thawed. The freeze-vial was wiped with 70% ethanol and cells were immediately pipetted into the 175 cm^2 tissue culture flask containing supplemented media. The cells were incubated overnight and the media was removed and replaced with fresh supplemented media the next day. The flask was incubated until flask became about 90% confluent This took anywhere from 5-7 days.

[0096] The flask was washed with 10 ml of sterile room temperature phosphate buffered saline (PBS). The cells were trypsinized by adding 5 ml of warmed Trypsin-EDTA (Invitrogen) to the flask of cells. The cells were then incubated for 2-3 minutes at 37 °C until cells begun to detach from the surface of the flask. An equal volume of supplemented media (5 ml) was added to the flask. All the cells were collected into 50 ml tube, and centrifuged at 1000 RPM for 5 minutes at 20° C. The supernatant was aspirated and the cell pellet was resuspended in 10 ml of supplemented media and the cells were counted. 1-3 million cells/flask were seeded into 5-7 tissue culture flasks (175 cm^2). Each flask contained 50 ml of supplemented media. The flasks were incubated until about 90% confluent. The passaging of the cells was repeated until enough cells have been grown for tumor implantation.

[0097] The above procedure for trypsinizing and centrifuging the cells were followed. The supernatant was aspirated and the cell pellet was resuspended in 10 ml of sterile PBS and the cells were counted. The cells were centrifuged and then resuspended with appropriate volume of sterile PBS for injection of correct number of cells needed for tumor implantation. In the case of MDA-435, 100 million cells were suspended with 2.0 ml of sterile PBS to a final concentration of 50 million cells/ml in order to inject 5 million cells in 0.1 ml/mouse.

[0098] Mice (CD-1 nu/nu) were obtained from Charles River Laboratories: nomenclature: Crl:CD-1-nuBR, Age: 6-8 weeks. The mice were allowed to acclimate for 1 week prior to their being used in an experimental procedure.

[0099] Implantation of the MDA-435 tumor cell suspension took place into the corpus adiposum of the female CD-1 nu/nu mouse. This fat body is located in the ventral abdominal viscera of the mouse. Tumor cells were implanted subsutaneously into the fat body located in the right quadrant of the abdomen at the juncture of the os coxae (pelvic bone) and the os femoris (femur). 5 million MDA-435 cells in 0.1 ml of sterile PBS were injected using 27 G (1/2 inch) needle. MDA-435 tumors developed 2-3 weeks after implantation.

[0100] Compound stock solutions were prepared by dissolving the compound in cell-culture-grade DMSO (dimethyl sulfoxide) at the desired concentration. This stock solution in DMSO was sonicated in an ultrasonic water bath until all the powder dissolved.

[0101] The Formulation Solvent was prepared as follows: 20% of Cremophore RH40 (Polyoxyl 40 Hydrogenated Castor Oil obtained from BASF corp.) in water was prepared by first heating 100 % Cremophore RH40 in a water bath at 50-60 °C until it liquefied and became clear. 10 ml of the 100 % Cremophore RH40 aliquoted into a conical centrifuge

tube containing 40 ml of sterile water (1:5 dilution of Cremophore RH40). The 20% Cremophore RH40 solution was reheated until it became clear again, and mixed by inverting the tube several times. This 20 % Cremophore RH40 solution was stored at room temperature, and was kept for up to 3 months.

[0102] Preparation of Dosing Solution for Compound Administration: The compound stock solution was diluted 1:10 with 20% Cremophore RH40: 1) 2.0 ml of 10 mg/ml dosing solution of Compound (1) was prepared by diluting 100 mg/ml Compound Stock solution with 1.8 ml of 20 % Cremophore RH40 water solution; and 2) a dosoing solution comprising 2.0 ml of 1 mg/ml of Paclitaxel (obtained from Sigma Chemical Co.) and 5 mg/ml of Compound (1) was obtained by mixing 0.1 ml of Compound 1 DMSO stock solution (50 mg/ml) and 0.1 ml of Paclitaxel DMSO stock solution (10 mg/ml) and diluting with 1.8 ml of 20 % Cremophore RH40 water solution. The final formulation for the dosing solution was 10% DMSO, 18% Cremophore RH40 and 72% water.

[0103] The Dosing Solution (Dosing Volume: 0.01 ml/gram =10 ml/ kg) was injected intravenously into the mice bearing MDA-435 human breast tumor.

PROTOCOL

[0104]

Group	Compounds	(Dose)
1	Vehicle Only	
2	Paclitaxel	(5 mg/kg)
3.	Compound (1)	(50 mg/kg)
4	Paclitaxel	(5 mg/kg) + Compund (1) (25 mg/kg)
5	Paclitaxel	(5mg/kg) + Compound (1) (50 mg/kg)

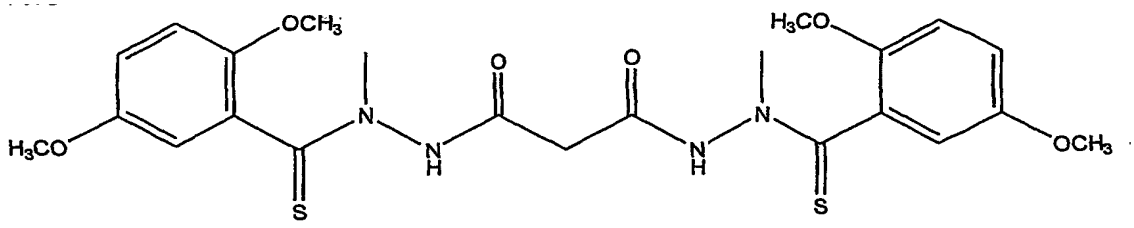
Dosing Schedule: 3 times a week (Monday, Wednesday, Friday) for 3 weeks 5 mice were used for each group

RESULTS

[0105] Figure 1 shows the effects of Compound (1) on enhancing anti-tumor activity of Paclitaxel (Taxol). As can be seen from Figure 1, Compound (1) significantly enhanced anti-tumor activity of Paclitaxel on human breast tumor MDA-435 in nude mice. Figure 2 shows the effects of Compound (1) and Paclitaxel on the body weight of nude mice bearing MDA-435 human breast tumor. As can be seen from Figure 2, Compound (1) significantly enhanced anti-tumor activity of Paclitaxel without increasing toxicity.

Example 13 - Compounds (1) and (2) Enhance the Anticancer Activity of Paclitaxel In *Vivo*

[0106]



Compound (2)

[0107] The protocol described in Example 12 was used to test Compounds (1) and (2) for their ability to enhance the anti-cancer activity of paclitaxel in mice, except as modified as described below.

PROTOCOL

[0108]

Group	Compounds	(Dose)
1	Vehicle Only	
2	Paclitaxel	(2 mg/kg)
3	Paclitaxel	(5 mg/kg)
4	Compound (1)	(80 mg/kg)
5	Compound (2)	(80 mg/kg)
6	Paclitaxel	(2 mg/kg) + Compound (1) (80 mg/kg)
7	Paclitaxel	(5 mg/kg) + Compound (1) (80 mg/kg)
8	Paclitaxel	(2 mg/kg) + Compound (2) (80 mg/kg)
9	Paclitaxel	(5 mg/kg) + Compound (2) (80 mg/kg)

Dosing Schedule: 3 times a week (Monday, Wednesday, Friday) for 3 weeks 5 mice were used for each group.

RESULTS

[0109]

Group	Average Tumor Volume (mm^3) on Day 23	% Tumor Growth
1	301.3	100
2	259.8	86
3	164.8	55
4	270.0	90
5	305.8	101
6	193.3	64
7	106.2	35
8	148.4	49
9	60.6	20

Compounds (1) and (2) significantly enhanced anti-tumor activity of Paclitaxel at both of 2 mg/kg and 5 mg/kg without increasing toxicity.

[0110] Example 14 - Compound (1) Enhances the Anticancer Activity of Paclitaxel *In Vivo* The protocol described in Example 12 was used to test Compound (1) for its ability to enhance the anti-cancer activity of paclitaxel in mice, except modified as described below.

PROTOCOL

[0111]

Group	Compounds	(Dose)
1	Vehicle Only	
2	Paclitaxel	(10 mg/kg)
3	Compound (1)	(50 mg/kg)
4	Paclitaxel	(10 mg/kg) + Compound (1) (25 mg/kg)

Dosing Schedule :
3 times a week (Monday, Wednesday, Friday) for 3 weeks 5 mice were used for each group

RESULTS

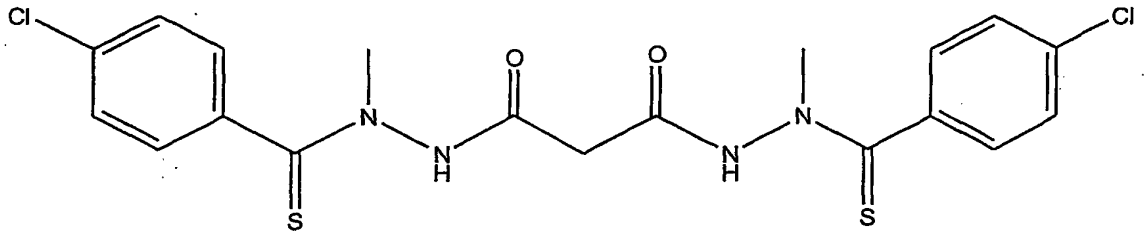
[0112]

Group	Average Tumor Volume [mm^3]	% Tumor Growth Inhibition on Day 48
1	752.2	-
2.	105.4	86 %
3	754.9	0 %
4	0.59	>99.9%

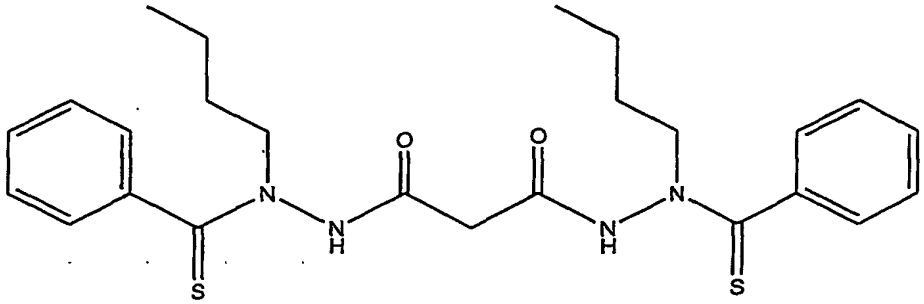
[0113] When 10 mg/kg of Paclitaxel was used, significant anti-tumor activity was observed. However, after drug treatment (Day 1~20) terminated, the tumor started growing to become 105 mm^3 volume on Day 43. On the other hand, average tumor volume after treatment of Paclitaxel (10 mg/kg) plus Compound (1) (25 mg/kg) was only 0.59 mm^3 with more than 99.9 % tumor growth inhibition.

Example 15 - Compounds (3)-(5) Enhance the Anticancer Activity of Paclitaxel *In Vivo*

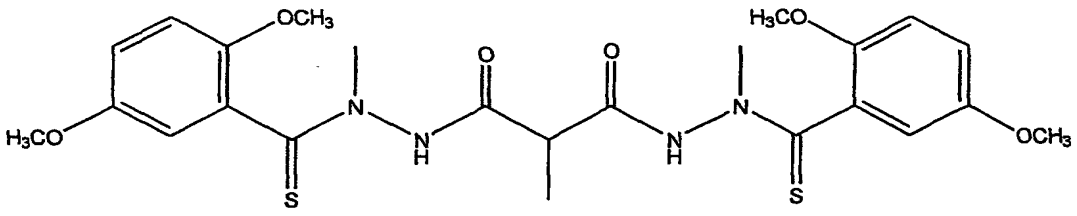
[0114]



Compound (3)



Compound (4)



Compound (5)

[0115] The protocol described in Example 12 was used to test Compounds (3)-(5) for their ability to enhance the anti-cancer activity of paclitaxel in mice, except modified as described below.

PROTOCOL

[0116]

Group	Compounds	(Dose)
1	Vehicle Only	
2	Paclitaxel	(5 mg/kg)
3	Paclitaxel	(5 mg/kg) + Compound (3) (50 mg/kg)
4	Paclitaxel	(5 mg/kg) + Compound (4) (100 mg/kg)
5	Paclitaxel	(5 mg/kg) + Compound (5)(100 mg/kg)

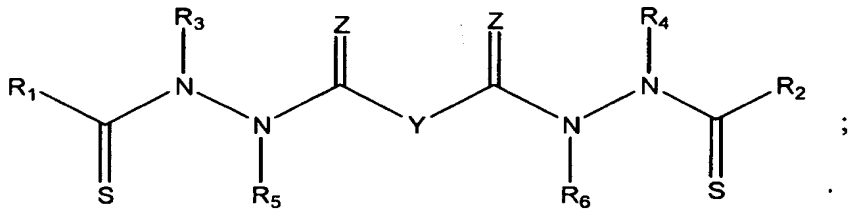
Dosing Schedule:
3 times a week (Monday, Wednesday, Friday) for 3 weeks 5 mice were used for each group
RESULTS

Group	Average % Tumor Growth Inhibition on Day 27
2	19
3	76
4	66
5	79

[0117] Compounds (3)-(5) demonstrated significant enhancing effects of Taxol anti-tumor activity.

Claims

1. A compound represented by the following structural formula:

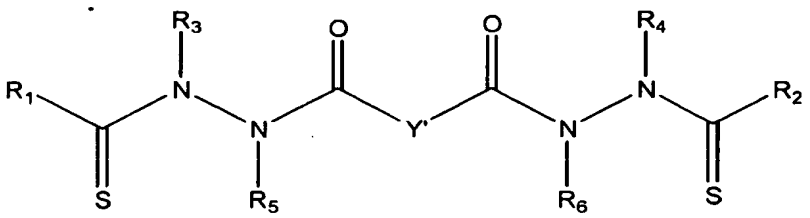


;

or a pharmaceutically acceptable salt thereof, wherein:

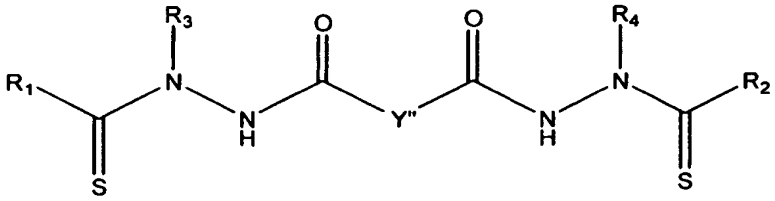
Y is a covalent bond or a substituted or unsubstituted straight chained hydrocarbyl group;
R_1 and R_2 are independently an aryl group or a substituted aryl group;
R_3 and R_4 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group;
R_5-R_6 are independently - H or an aliphatic group; and
Z is =O or =S;
provided that when Y is -CH_2-, R_3 and R_4 are both phenyl and R_5-R_6 are all - H, then R_1 and R_2 are not both phenyl.

2. The compound of Claim 1 wherein the compound is represented by the following structural formula:



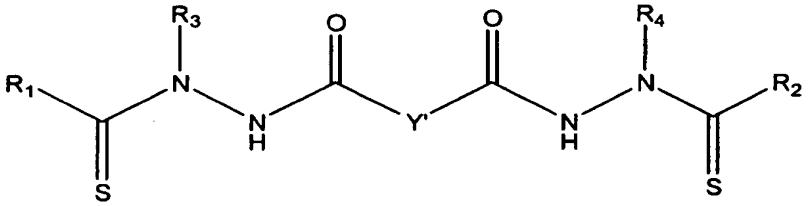
wherein Y' is a covalent bond or $-CR_7R_8-$ and R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8, taken together, are a C2-C6 substituted or unsubstituted alkylene group.

3. The compound of Claim 2 wherein the compound is represented by the following structural formula:



wherein Y" is a covalent bond or $-CH_2-$.

4. The compound of Claim 2 wherein the compound is represented by the following structural formula:



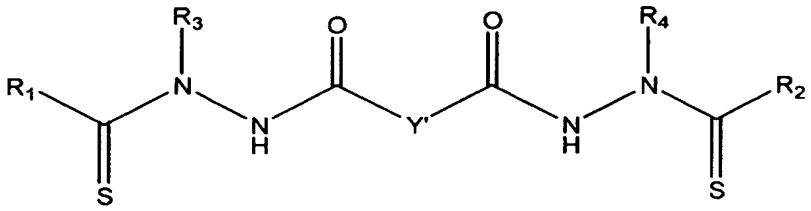
wherein Y' is a covalent bond or $-CR_7R_8-$.

5. The compound of Claim 4 wherein R_1 and R_2 are both aryl or substituted aryl groups and R_3 and R_4 are both a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group or a substituted C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group.

6. The compound of Claim 5 wherein R_1 and R_2 are both phenyl or substituted phenyl and R_3 and R_4 are both methyl, ethyl, phenyl, or thienyl.

7. The compound of Claim 6 wherein R_7 and R_8 are both methyl or wherein R_7 and R_8, taken together, are propylene or butylenes, or R_7 is -H and R_8 is lower alkyl, thienyl, phenyl or benzyl.

8. A compound of claim 1 represented by the following structural formula:

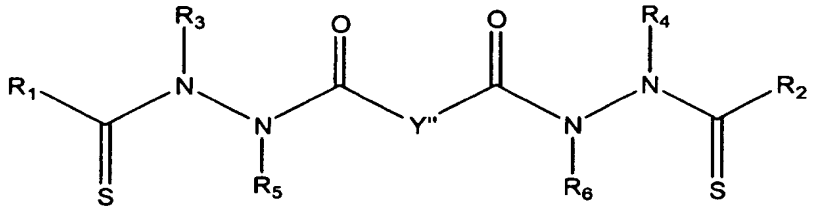


or a physiologically acceptable salt thereof, wherein:

Y' is a covalent bond or $-CR_7R_8-$;
R_1 and R_2 are both a substituted or unsubstituted aryl group;
R_3 and R_4 are both -H, methyl or ethyl; and
R_7 is -H and R_8 is -H or methyl.

9. The compound of Claim 8 wherein R_1 and R_2 are both phenyl optionally substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$,$-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$; $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$,$-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, alkyl group, non-aromatic heterocyclic group, benzyl group or aryl group wherein R^a-R^d are each independently an alkyl group, benzyl, or aromatic group or,$-NR^aR^d$, taken together, can also form an unsubstituted non-aromatic heterocyclic group.

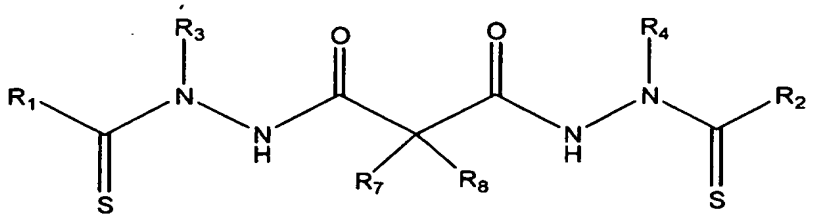
10. The compound of Claim 2 wherein the compound is represented by the following structural formula:



wherein Y" is a covalent bond or $-CH_2$.

11. The compound of Claim 10 wherein R_5 and R_6 are both a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group or a phenyl group.

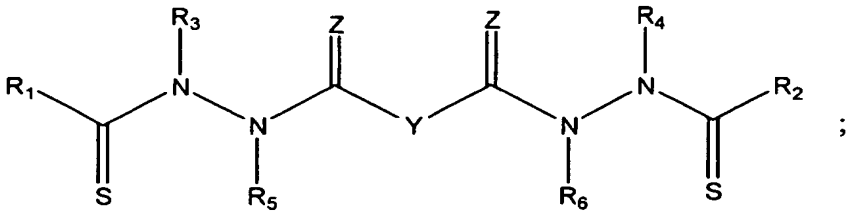
12. A compound of claim 1 represented by the following structural formula:



or a physiologically acceptable salt thereof, wherein

a) R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
b) R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_7 and R_8 are both -H;
c) R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
d) R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
e) R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
f) R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_7 is methyl; R_8 is -H;
g) R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
h) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
i) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
j) R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_1 and R_8 are both -H;
k) R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_1 and R_8 are both -H;
1) R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
m) R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
n) R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
o) R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
p) R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
q) R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
r) R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is-H;
s) R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
t) R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
u) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
v) R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H; and
w) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following structural formula:

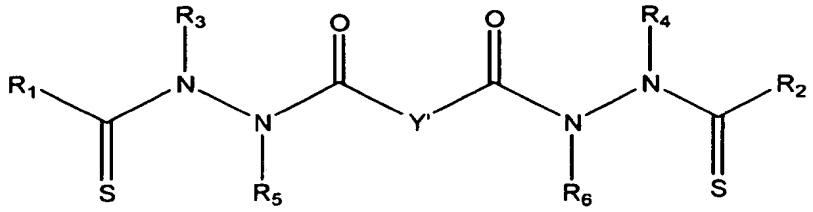


;

or a physiologically acceptable salt thereof, wherein:

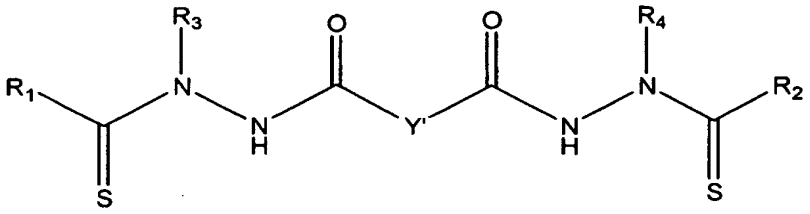
Y is a covalent bond or a substituted or unsubstituted straight chained hydrocarbyl group;
R_1 and R_2 are independently an aryl group or a substituted aryl group,
R_3 and R_4 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group;
R_5-R_6 are independently - H or an aliphatic group; and
Z is =O or =S.

14. The pharmaceutical composition of Claim 13 wherein the compound is represented by the following structural formula:



wherein Y' is a covalent bond or $-CR_7R_8-$ and R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8, taken together, are a C2-C6 substituted or unsubstituted alkylene group.

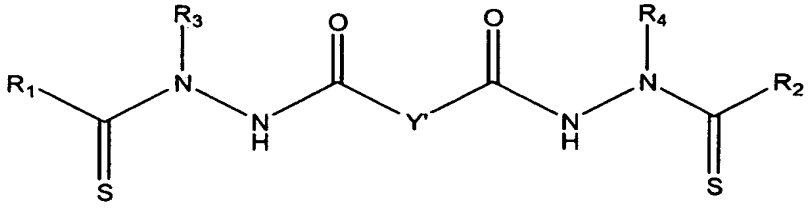
15. The pharmaceutical composition of Claim 14 wherein the compound is represented by the following structural formula:



wherein Y' is a covalent bond or $-CR_7R_8-$.

16. The pharmaceutical composition of Claim 15 wherein R_1 and R_2 are both phenyl or substituted phenyl; R_3 and R_4 are methyl, ethyl, phenyl, or thienyl; and R_7 and R_8 are both methyl; R_7 and R_8, taken together, are propylene or butylenes; or R_7 is -H and R_8 is lower alkyl, thienyl, phenyl or benzyl.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following structural formula:



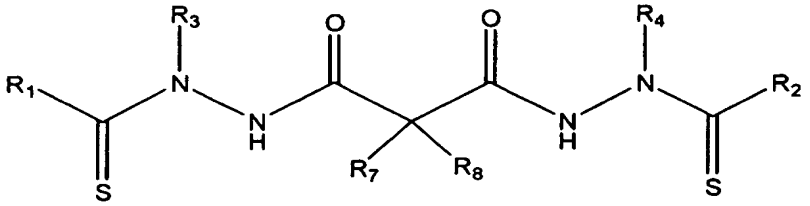
or a physiologically acceptable salt thereof, wherein:

Y' is a covalent bond or $-CR_7R_8-$;
R_1 and R_2 are both a substituted or unsubstituted aryl group;
R_3 and R_4 are both -H, methyl or ethyl; and
R_7 is -H and R_8 is -H or methyl.

18. The pharmaceutical composition of Claim 17 wherein R_1 and R_2 are both phenyl optionally substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, - OR^a, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, - $COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, - $NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$,- $NH-C(=NH)-N(R^aR^b)$,

-NH-C(=NR^c)-NH_2, -NH-C(=NR^c)-NHR^a -NH-C(=NR^c)-N(R^aR^b), -NR^dH-C(=NH)-NH_2, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b), -NR^d-C(=NR^c)-NH_2, -NR^d-C(=NR^c)-NHR^a -NR^d-C(=NR^c)-N(R^aR^b), - $NHNH_2$, -$NHNHR^a$, -NHR^aR^b, -SO_2NH_2, -SO_2NHR^a, -$SO_2NR^aR^b$, -CH=CHR^a, - CH=CR^aR^b, -CR^c=CR^aR^b,-CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -S(O)R^a, - $S(O)_2R^a$ alkyl groups, non-aromatic heterocyclic group, benzyl group or aryl group wherein R^a-R^d are each independently an alkyl group, benzyl, or aromatic group, or,-NR^aR^d , taken together, can also form an unsubstituted non-aromatic heterocyclic group.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following structural formula:

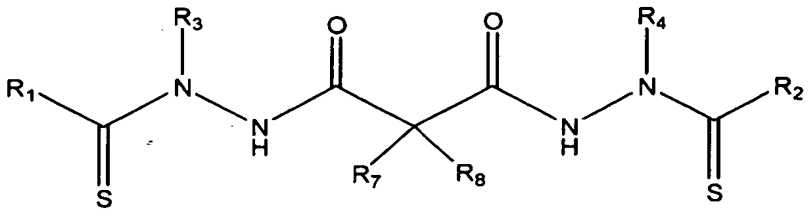


;

or physiologically acceptable salt thereof, wherein:

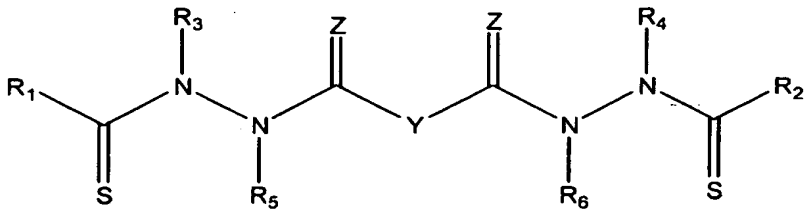
a) R_1 and R_2 are both phenyl; R_3 and R_4 are both phenyl; R_7 and R_8 are both -H;
b) R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_7 and R_8 are both -H;
c) R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
d) R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
e) R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
f) R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_7 is methyl; R_8 is -H;
g) R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
h) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
i) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
j) R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
k) R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
l) R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
m) R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
n) R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
o) R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
p) R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
q) R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
r) R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H;
s) R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
t) R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
u) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;
v) R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H; and
w) R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_7 is methyl; R_8 is -H.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following structural formula:



wherein R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H;

21. Use of a compound represented by the following structural formula:

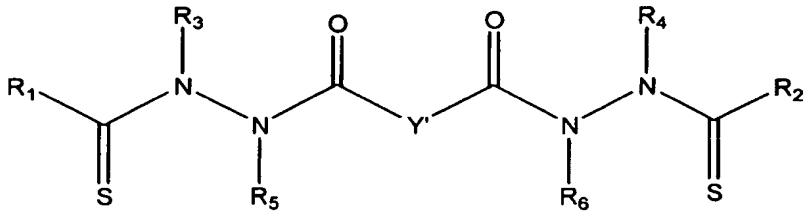


or a physiologically acceptable salt thereof, wherein:

Y is a covalent bond, or a substituted or unsubstituted hydrocarbyl group;
R_1 and R_2 are independently an aryl group or a substituted aryl group;
R_3 and R_4 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group;
R_5-R_6 are independently - H or an aliphatic group;
and Z is =O or =S,

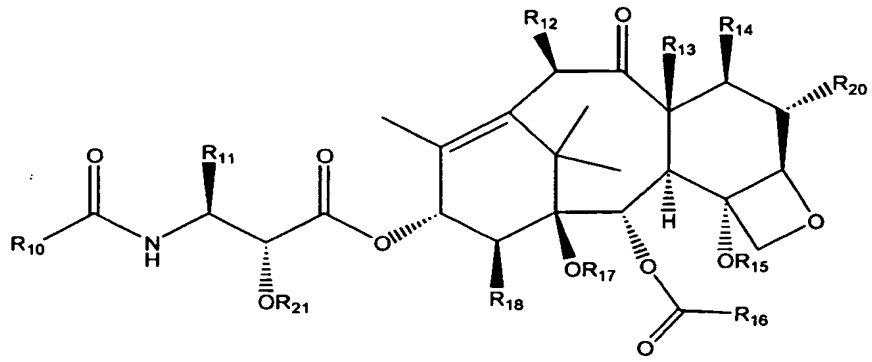
for the production of a medicament to enhance the anticancer activity of taxol or a taxol analog.

22. The use according to Claim 21 wherein the compound is represented by the following structural formula:

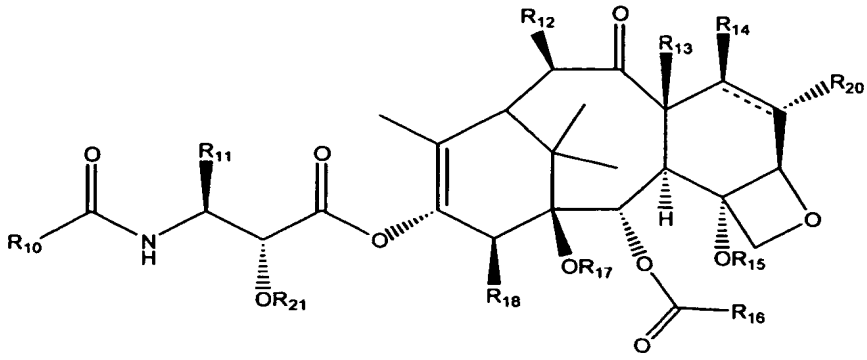


wherein Y' is a covalent bond or -CR_7R_8- and R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8, taken together, are a C2-C6 substituted or unsubstituted alkylene group.

23. The use according to Claim 22 wherein the taxol analog is represented by a structural formula selected from:



or



wherein:

R_{10} is a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, a substituted C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, a phenyl group, a substituted phenyl group, $-SR_{19}$, $-NHR_{19}$ or $-OR_{19}$;

$R_{11}$is a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, a substituted C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, an aryl group or a substituted aryl group;

R_{12} is -H, -OH, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, -O-C(O)-(lower alkyl), -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-$(lower alkyl) $-S-CH_2-O-$(lower alkyl);

R_{13} is -H, $-CH_3$, or, taken together with R_{14} $-CH_2-$;

R_{14} is -H, -OH, lower alkoxy, -O-C(O)-(lower alkyl), substituted lower alkoxy, -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-P(O)(OH)_2$, $-O-CH_2-O-$(lower alkyl), $-O-CH_2-S-$(lower alkyl) or, taken together with R_{20}, a double bond;

R_{15} -H, lower acyl, lower alkyl, substituted lower alkyl, alkoxymethyl, alkthiomethyl, -OC(O)-O(lower alkyl), -OC(O)-O(substituted lower alkyl), -OC(O)-NH(lower alkyl) or -OC(O)-NH(substituted lower alkyl);

R_{16} is phenyl or substituted phenyl;

R_{17} is -H, lower acyl, substituted lower acyl, lower alkyl, substituted, lower alkyl, (lower alkoxy)methyl or (lower alkyl)thiomethyl;

R_{18} -H, $-CH_3$ or, taken together with R_{17} and the carbon atoms to which R_{17} and R_{18} are bonded, a five or six membered a non-aromatic heterocyclic ring;

R_{19} is a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, a substituted C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group, a phenyl group, a substituted phenyl group;

R_{20} is -H or a halogen; and

R_{21} is -H, lower alkyl, substituted lower alkyl, lower acyl or substituted lower acyl, wherein the term "lower alkyl" refers to a C1-C20 straight chained or branched alkyl group or a C3-C8 cyclic alkyl group and the terms "lower alkoxy", "lower acyl", "(lower alkoxy)methyl" and "(lower alkyl)thiomethyl" mean to -O-(lower alkyl), -C(O)-(lower

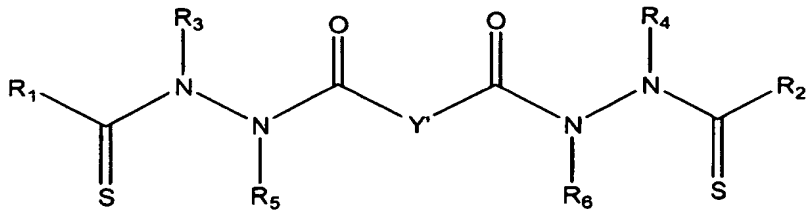
alkyl), -CH_2-(lower alkyl) and -CH_2-S-(lower alkyl), respectively, and the terms "substituted lower alkoxy" and "substituted lower acyl" mean -O-(substituted lower alkyl) and -C(O)-(substituted lower alkyl), respectively.

24. The use according to Claim 23 wherein:

R_{10} is phenyl, *tert*-butoxy, -S-CH_2-CH-$(CH_3)_2$, -S-$CH(CH_3)_3$, -S-$(CH_2)_3CH_3$, - O-$CH(CH_3)_3$, -NH-$CH(CH_3)_3$, -CH=$C(CH_3)_2$ or *para*-chlorophenyl;
R_{11} is phenyl, $(CH_3)_2CHCH_2$-, -2-furanyl, cyclopropyl or *para*-toluyl;
R_{12} is -H, -OH, CH_3CO- or -$(CH_2)_2$-*N* morpholino;
R_{13} is methyl, or, R_{13} and R_{14}, taken together, are -CH_2-;
R_{14} is -H, -CH_2SCH_3 or -CH_2-O-P(O)$(OH)_2$;
R_{15} is CH_3CO-;
R_{16} is phenyl;
R_{17} -H, or, R_{17} and R_{18}, taken together, are -O-CO-O-;
R_{18} is -H;
R_{20} is -H or -F; and
R_{21} is -H, -C(O)-CHBr-$(CH_2)_{13}$-CH_3 or -C(O)-$(CH_2)_{14}$-CH_3; -C(O)-CH_2-CH(OH)-COOH, -C(O)-CH_2-O-C(O)-$CH_2CH(NH_2)$-$CONH_2$, -C(O)-CH_2-O-$CH_2CH_2OCH_3$ or -C(O)-O-C(O)-CH_2CH_3.

25. The use according to Claim 22 wherein a taxol analog is comprised in the medicament the taxol analog is represented by a structure shown in any one of Figures 5-25, the taxol analog is the copolymer of *N*-(2-hydroxypropyl)methacrylamide,methacryloylglycine-2-hydroxypropylamide and [2aR[2α,4β,4β,6β,9α(2R,3S),11β,12α,12α,12α]]-6,12b-diacetoxy-9-[3-benzamido-2-(methacryloyl-glycyl-L-phenylalanyl-L-leucyl.glycyloxy)-3-phenylpropionyloxy]-12-benzoyloxy-4, 11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a, 12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benz[1,2-b]oxet-5-one, or the subject is administered taxol or taxotere.

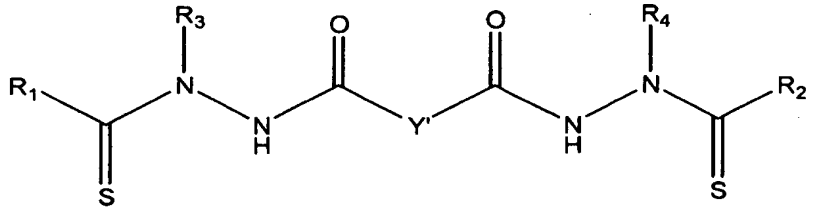
26. The use according to Claim 23 wherein the compound is represented by the following structural formula:



;

wherein Y' is a covalent bond or -CR_7R_8-.

27. The use according to Claim 23 wherein the compound is represented by the following structural formula:

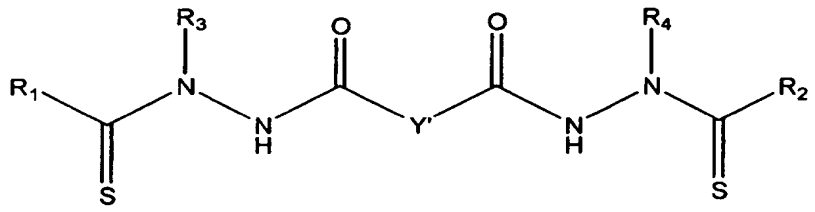


;

wherein Y' is a covalent bond or -CR_7R_8-.

28. The use according to Claim 27 wherein R_1 and R_2 are both aryl or substituted aryl groups and R_3 and R_4 are both a C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group or a substituted C1-C20 straight chain or branched alkyl group or a C3-C8 cyclic alkyl group.

29. Use of a compound represented by the following structural formula:



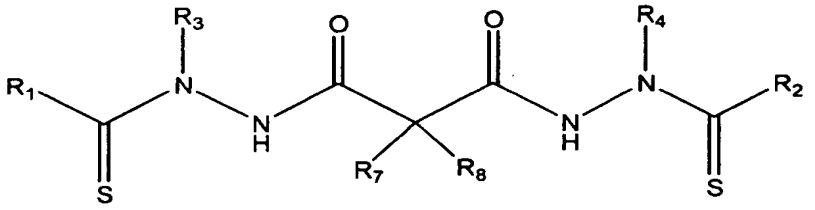
;

or a physiologically acceptable salt thereof, wherein:

Y' is a covalent bond or $-CR_7R_8-$;
R_1 and R_2 are both a substituted or unsubstituted aryl group;
R_3 and R_4 are both -H, methyl or ethyl; and
R_7 is -H and R_8 is -H or methyl, for the production of a medicament to enhance the anticancer activity of taxol or a taxol analog.

30. The use according to Claim 29 wherein R_1 and R_2 are both phenyl optionally substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, - CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, - $CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$,$-NHCON(R^aR^b)$,- NR^cCONH_2, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, - $C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$,$-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH$, $-SO_2NHR^a$,$-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$,$-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, alkyl groups, non-aromatic heterocyclic group, benzyl group or aryl group wherein R^a-R^d are each independently an alkyl group, benzyl, or aromatic group, or,$-NR^aR^d$, taken together, can also form an unsubstituted non-aromatic heterocyclic group.

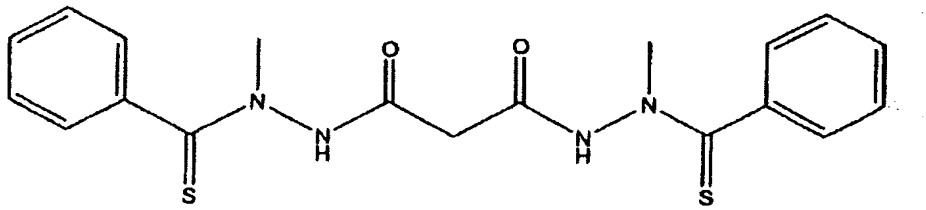
31. Use of a compound represented by the following structural formula:



;

or physiologically acceptable salt thereof, wherein R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_7 and R_8 are both -H,
for the production of a medicament to enhance the anticancer activity of taxol or a taxol analog.

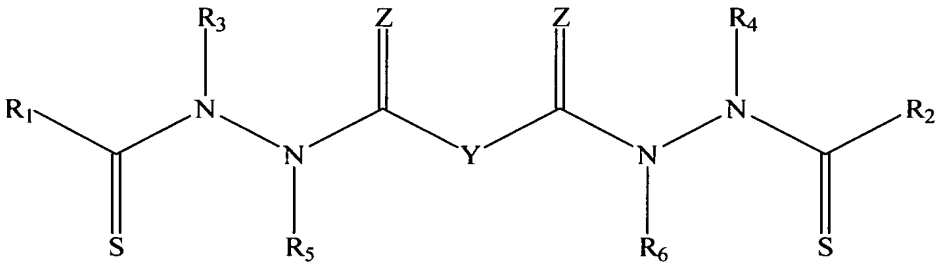
32. A compound of claim 1 wherein the compound is represented by the following structural formula:



or a
physiologically acceptable salt thereof.

Patentansprüche

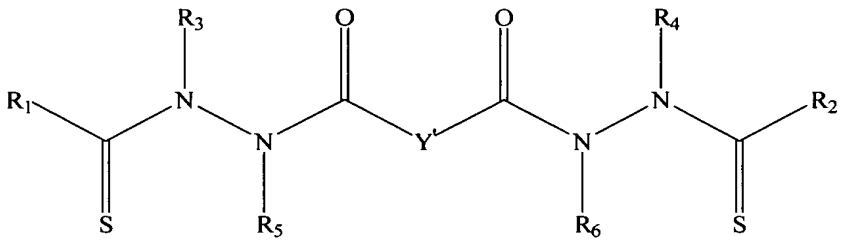
1. Eine Verbindung, dargestellt durch die folgende Strukturformel:



oder ein pharmazeutisch akzeptables Salz davon, wobei

Y eine kovalente Bindung ist oder eine substituierte oder unsubstituierte geradkettige Kohlenwasserstoffgruppe,
R_1 und R_2 unabhängig voneinander eine Arylgruppe oder eine substituierte Arylgruppe sind,
R_3 und R_4 unabhängig voneinander - H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine Arylgruppe oder eine substituierte Arylgruppe sind,
R_5-R_6 unabhängig voneinander - H oder eine aliphatische Gruppe sind und
Z =O oder =S ist,
unter der Voraussetzung, dass wenn Y $-CH_2-$ ist, R_3 und R_4 beide Phenyl sind und R_5-R_6 alle -H sind, dann R_1 und R_2 nicht beide Phenyl sind.

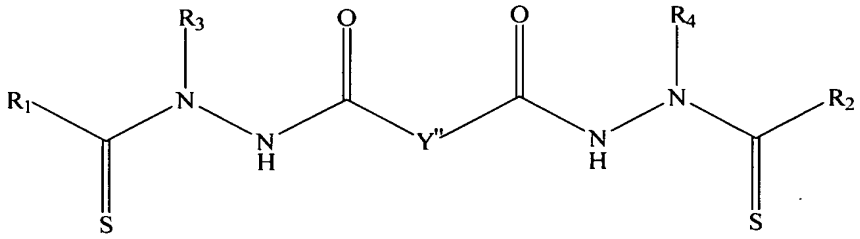
2. Die Verbindung aus Anspruch 1, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y' eine kovalente Bindung ist oder $-CR_7R_8-$ und R_7 und R_8 jeweils unabhängig voneinander -H, eine alipha-

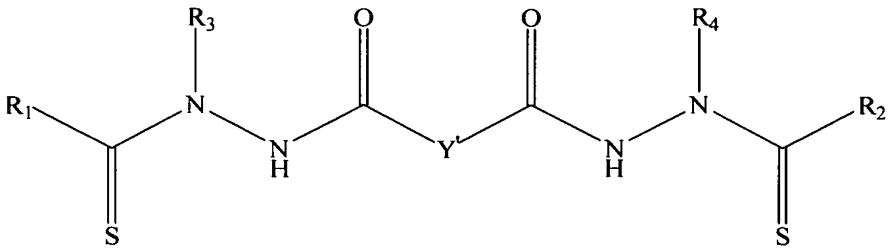
tische oder substituierte aliphatische Gruppe sind, oder R_7 -H und R_8 eine substituierte oder unsubstituierte Arylgruppe ist, oder R_7 und R_8 zusammengenommen eine C2-C6 substituierte oder unsubstituierte Alkylengruppe sind.

3. Die Verbindung aus Anspruch 2, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y" eine kovalente Bindung ist oder $-CH_2-$.

4. Die Verbindung aus Anspruch 2, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



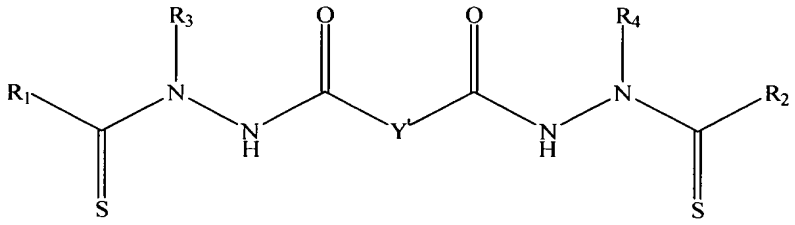
wobei Y' eine kovalente Bindung ist oder $-CR_7R_8-$.

5. Die Verbindung aus Anspruch 4, wobei R_1 und R_2 beide Aryl- oder substituierte Arylgruppen sind und R_3 und R_4 beide C1-C20 geradkettige oder verzweigte Alkylgruppen sind, oder eine C3-C8 cyclische Alkylgruppe, oder eine substituierte C1-C20 geradkettige oder verzweigte Alkylgruppe, oder eine C3-C8 zyklische Alkylgruppe.

6. Die Verbindung aus Anspruch 5, wobei R_1 und R_2 beide Phenyl oder substituiertes Phenyl sind und R_3 und R_4 beide Methyl, Ethyl, Phenyl oder Thienyl sind.

7. Die Verbindung aus Anspruch 6, wobei R_7 und R_8 beide Methyl sind, oder wobei R_7 und R_8 zusammen genommen Propylen oder Butylene sind, oder R_7 -H ist und R_8 ein niederes Alkyl, Thienyl, Phenyl oder Benzyl ist.

8. Eine Verbindung gemäß Anspruch 1, repräsentiert durch die folgende Strukturformel:

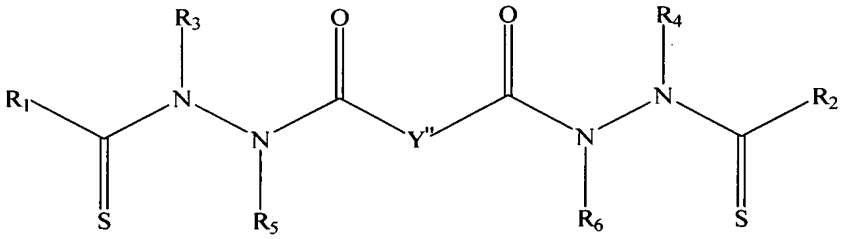


oder ein physiologisch akzeptables Salz davon, wobei:

Y' eine kovalente Bindung oder $-CR_7R_8-$ ist,
R_1 und R_2 beide eine substituierte oder unsubstituierte Arylgruppe sind,
R_3 und R_4 beide -H, Methyl oder Ethyl sind, und
R_7 -H und R_8 -H oder Methyl ist.

9. Die Verbindung aus Anspruch 8, wobei R_1 und R_2 beide Phenyl sind, wahlweise substituiert mit einer oder mehreren Gruppen, ausgewählt aus -OH, -Br, -Cl, -J, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$ $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, Alkylgruppe, nicht-aromatischer heterocyclischer Gruppe, Benzyl- oder Arylgruppe, wobei R^a-R^d jeweils unabhängig voneinander eine Alkylgruppe, Benzylgruppe oder aromatische Gruppe sind, oder $-NR^aR^d$ zusammen genommen auch eine unsubstituierte nicht-aromatische heterocyclische Gruppe bilden kann.

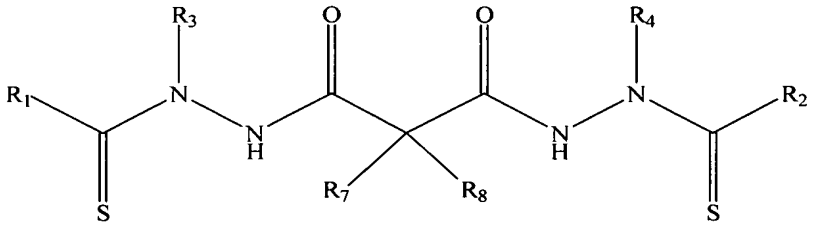
10. Die Verbindung aus Anspruch 2, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y" eine kovalente Bindung ist oder $-CH_2$.

11. Die Verbindung aus Anspruch 10, wobei R_5 und R_6 beide eine C1-C20 geradkettige oder verzweigte Alkylgruppe sind oder eine C3-C8 cyclische Alkylgruppe oder eine Phenylgruppe.

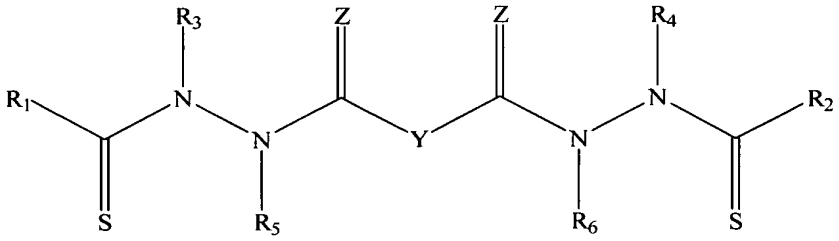
12. Eine Verbindung gemäß Anspruch 1, repräsentiert durch die folgende Strukturformel:



oder ein physiologisch akzeptables Salz davon, wobei

a) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
b) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Ethyl sind, R_7 und R_8 beide -H sind,
c) R_1 und R_2 beide 4-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
d) R_1 und R_2 beide 4-Methoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
e) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
f) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Ethyl sind, R_7 Methyl ist, R_8 -H ist,
g) R_1 und R_2 beide 4-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
h) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
i) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
j) R_1 und R_2 beide 3-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
k) R_1 und R_2 beide 3-Fluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
l) R_1 und R_2 beide 4-Chlorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H sind,
m) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
n) R_1 und R_2 beide 3-Methoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
o) R_1 und R_2 beide 2,3-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
p) R_1 und R_2 beide 2,3-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
q) R_1 und R_2 beide 2,5-Difluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
r) R_1 und R_2 beide 2,5-Difluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
s) R_1 und R_2 beide 2,5-Dichlorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
t) R_1 und R_2 beide 2,5-Dimethylphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
u) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
v) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind, und
w) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist und R_8 -H ist.

13. Eine pharmazeutische Zusammensetzung aus einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel und einer Verbindung, repräsentiert durch die folgende Strukturformel:

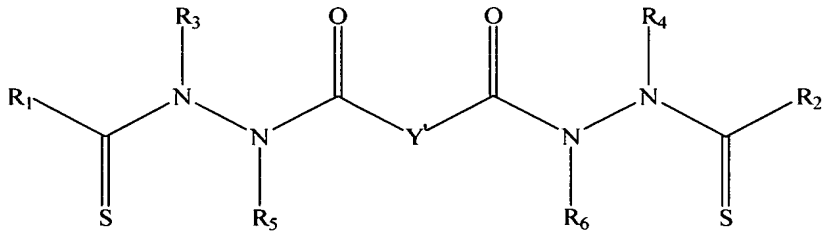


oder einem physiologisch akzeptablen Salz davon, wobei:

Y eine kovalente Bindung ist oder eine substituierte oder unsubstituierte geradkettige Kohlenwasserstoffgruppe,
R_1 und R_2 unabhängig voneinander eine Arylgruppe oder eine substituierte Arylgruppe sind,
R_3 und R_4 unabhängig voneinander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine Arylgruppe oder eine substituierte Arylgruppe sind,

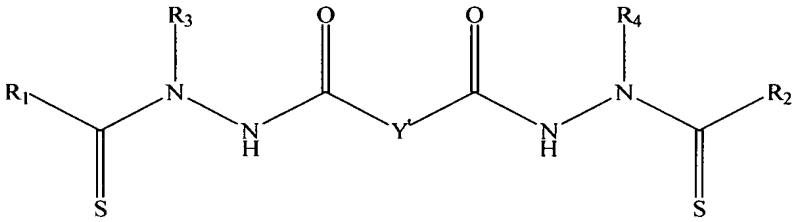
R_5-R_6 unabhängig voneinander -H oder eine aliphatische Gruppe sind, und
Z =O oder =S ist.

14. Die pharmazeutische Zusammensetzung aus Anspruch 13, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y' eine kovalente Bindung ist oder -CR_7R_8- und R_7 und R_8 jeweils unabhängig voneinander -H, eine aliphatische oder substituierte aliphatische Gruppe sind, oder R_7 -H ist und R_8 eine substituierte oder unsubstituierte Arylgruppe, oder R_7 und R_8 zusammen genommen eine C2-C6 substituierte oder unsubstituierte Alkylengruppe bilden.

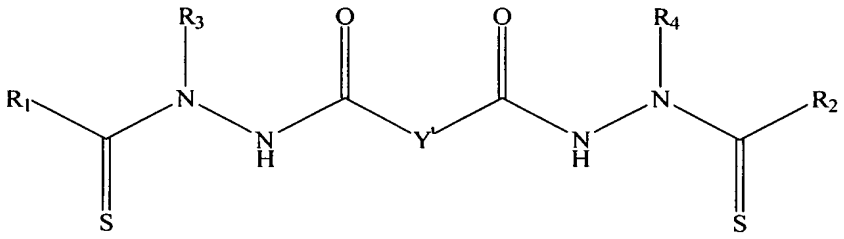
15. Die pharmazeutische Zusammensetzung aus Anspruch 14, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y' eine kovalente Bindung ist oder -CR_7R_8-.

16. Die pharmazeutische Zusammensetzung aus Anspruch 15, wobei R_1 und R_2 beide Phenyl oder substituiertes Phenyl sind, R_3 und R_4 Methyl, Ethyl, Phenyl oder Thienyl sind, und R_7 und R_8 beide Methyl sind, R_7 und R_8 zusammen genommen Propylen oder Butylen sind, oder R_7 -H und R_8 niederes Alkyl, Thienyl, Phenyl oder Benzyl ist.

17. Eine pharmazeutische Zusammensetzung aus einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel und einer Verbindung, repräsentiert durch die folgende Strukturformel:

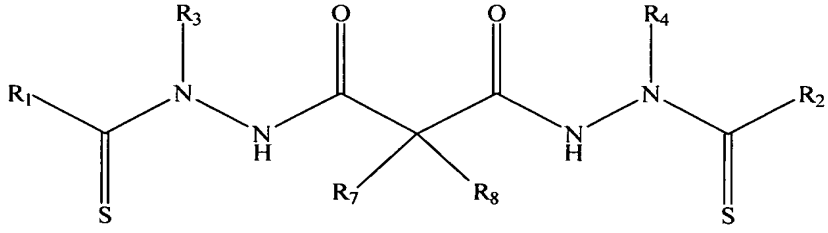


oder einem physiologisch akzeptablen Salz davon, wobei:

Y' eine kovalente Bindung ist oder $-CR_7R_8-$,
R_1 und R_2 beide eine substituierte oder unsubstituierte Arylgruppe sind,
R_3 und R_4 beide -H, Methyl oder Ethyl sind, und
R_7 -H ist und R_8 -H oder Methyl ist.

18. Die pharmazeutische Zusammensetzung aus Anspruch 17, wobei R_1 und R_2 beide Phenyl sind, wahlweise substituiert mit einer oder mehr Gruppen, ausgewählt aus -OH, -Br, -Cl, -J, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, Alkylgruppe, nicht-aromatischer heterocyclischer Gruppe, Benzylgruppe oder Arylgruppe, wobei R^a-R^d jeweils unabhängig voneinander eine Alkylgruppe, Benzylgruppe oder aromatische Gruppe sind oder $-NR^aR^d$ zusammen genommen auch eine unsubstituierte nicht-aromatische heterocyclische Gruppe bilden können.

19. Eine pharmazeutische Zusammensetzung aus einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel und einer Verbindung, repräsentiert durch die folgende Strukturformel:

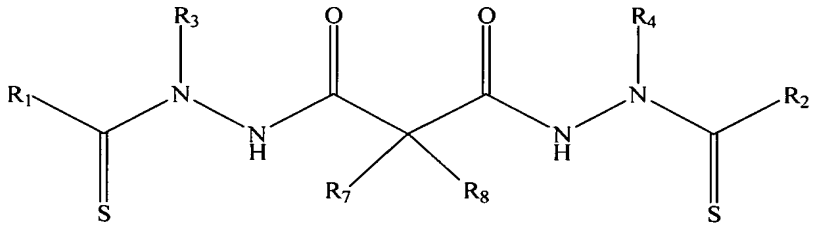


oder einem physiologisch akzeptablen Salz davon, wobei:

a) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Phenyl sind, R_7 und R_8 beide -H sind,
b) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Ethyl sind, R_7 und R_8 beide -H sind,
c) R_1 und R_2 beide 4-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
d) R_1 und R_2 beide 4-Methoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
e) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
f) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Ethyl sind, R_7 Methyl ist, R_8 -H ist,
g) R_1 und R_2 beide 4-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
h) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
i) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,

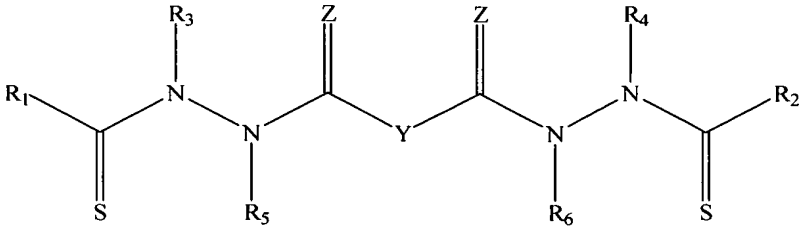
j) R_1 und R_2 beide 3-Cyanophenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
k) R_1 und R_2 beide 3-Fluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
l) R_1 und R_2 beide 4-Chlorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H sind,
m) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
n) R_1 und R_2 beide 3-Methoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
o) R_1 und R_2 beide 2,3-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
p) R_1 und R_2 beide 2,3-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
q) R_1 und R_2 beide 2,5-Difluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
r) R_1 und R_2 beide 2,5-Difluorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist, R_8 -H ist,
s) R_1 und R_2 beide 2,5-Dichlorphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
t) R_1 und R_2 beide 2,5-Dimethylphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
u) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind,
v) R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind, und
w) R_1 und R_2 beide 2,5-Dimethoxyphenyl sind, R_3 und R_4 beide Methyl sind, R_7 Methyl ist und R_8 -H ist.

20. Eine pharmazeutische Zusammensetzung aus einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel und einer Verbindung, repräsentiert durch die folgende Strukturformel:



wobei R_1 und R_2 beide Phenyl sind, R_3 und R_4 beide Methyl sind, R_7 und R_8 beide -H sind.

21. Verwendung einer Verbindung, repräsentiert durch die folgende Strukturformel:

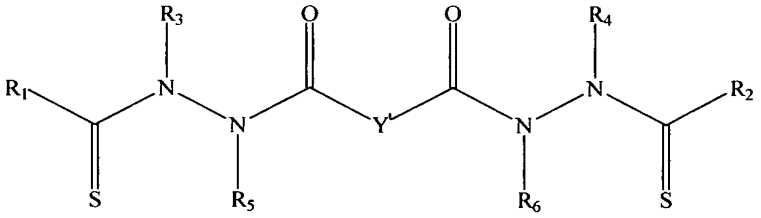


oder eines physiologisch akzeptablen Salzes davon, wobei:

Y eine kovalente Bindung ist oder eine substituierte oder unsubstituierte Kohlenwasserstoffgruppe,
R_1 und R_2 unabhängig voneinander eine Arylgruppe oder eine substituierte Arylgruppe sind,
R_3 und R_4 unabhängig voneinander -H, eine aliphatische Gruppe, eine substituierte aliphatische Gruppe, eine Arylgruppe oder eine substituierte Arylgruppe sind,
R_5-R_6 unabhängig voneinander -H oder eine aliphatische Gruppe ist, und
Z =O oder =S ist,

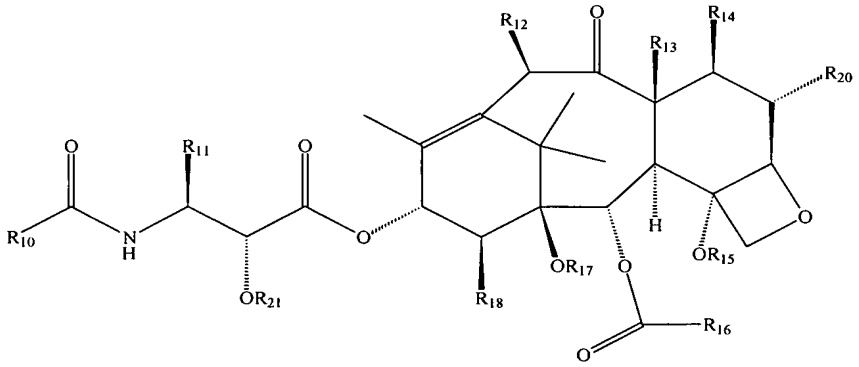
für die Herstellung eines Medikaments zur Erhöhung der Antikrebsaktivität von Taxol oder einem Taxolanalogen.

22. Die Verwendung gemäß Anspruch 21, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:

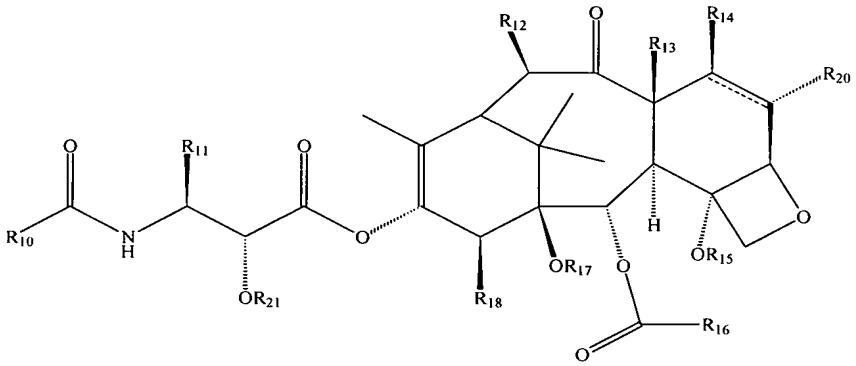


wobei Y' eine kovalente Bindung ist oder $-CR_7R_8-$ und R_7 und R_8 jeweils unabhängig voneinander -H, eine aliphatische oder substituierte aliphatische Gruppe sind, oder R_7 -H ist und R_8 eine substituierte oder unsubstituierte Arylgruppe ist, oder R_7 und R_8 zusammen genommen eine C2-C6 substituierte oder unsubstituierte Alkylengruppe ist.

23. Die Verwendung gemäß Anspruch 22, wobei das Taxolanaloge repräsentiert wird durch eine Strukturformel, ausgewählt aus:



oder



wobei:

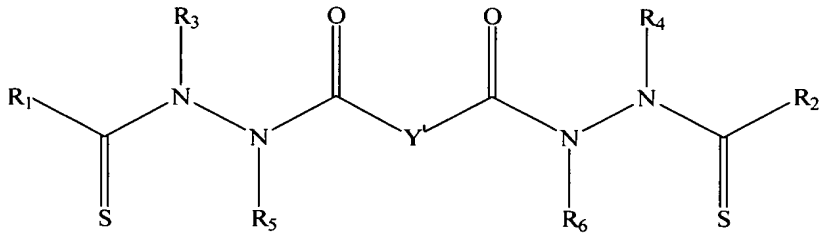
R_{10} eine C1-C20 geradkettige oder verzweigte Alkylgruppe oder eine C3-C8 cyclische Alkylgruppe ist, eine substituierte C1-C20 geradkettige oder verzweigte Alkylgruppe, oder eine C3-C8 cyclische Alkylgruppe, eine Phenylgruppe, eine substituierte Phenylgruppe, $-SR_{19}$, $-NHR_{19}$ oder $-OR_{19}$,
R_{11} eine C1-C20 geradkettige oder verzweigte Alkylgruppe oder eine C3-C8 cyclische Alkylgruppe ist, eine

substituierte C1-C20 geradkettige oder verzweigte Alkylgruppe oder eine C3-C8 cyclische Alkylgruppe, eine Arylgruppe oder eine substituierte Arylgruppe,
R_{12} -H, -OH, niederes Alkyl, substituiertes niederes Alkyl, niederes Alkoxy, substituiertes niederes Alkoxy, -O-C(O)-(niederes Alkyl), -O-C(O)-substituiertes niederes Alkyl), -O-CH_2-O-(niederes Alkyl), -S-CH_2-O-(niederes Alkyl) ist,
R_{13} -H, -CH_3 oder zusammen mit R_{14} -CH_2- ist,
R_{14} -H, -OH, niederes Alkyl, -O-C(O)-(niederes Alkyl), substituiertes niederes Alkoxy, -O-C(O)-(substituiertes niederes Alkyl), -O-CH_2-O-P(O)$(OH)_2$, -O-CH_2-O-(niederes Alkyl), -O-CH_2-S-(niederes Alkyl) oder zusammen mit R_{20} eine Doppelbindung ist,
R_{15} -H, niederes Acyl, niederes Alkyl, substituiertes niederes Alkyl, Alkoxymethyl, Alkthiomethyl, -OC(O)-O (niederes Alkyl), -OC(O)-O(substituiertes niederes Alkyl), -OC(O)-NH(niederes Alkyl) oder -OC(O)-NH(substituiertes niederes Alkyl) ist,
R_{16} Phenyl oder substituiertes Phenyl ist,
R_{17} -H, niederes Acyl, substituiertes niederes Acyl, niederes Alkyl, substituertes niederes Alkyl, (niederes Alkoxy) Methyl oder (niederes Alkyl)Thiomethyl ist,
R_{18} -H, -CH_3 oder zusammen genommen mit R_{17} und den Kohlenstoffatomen, an welche R_{17} und R_{18} gebunden sind, einen fünf- oder sechsgliedrigen nichtaromatischen heterocyclischen Ring bildet,
R_{19} eine C1-C20 geradkettige oder verzweigte Alkylgruppe ist oder eine C3-C8 cyclische Alkylgruppe, eine substituierte C1-C20 geradkettige oder verzeigte Alkylgruppe oder eine C3-C8 cyclische Alkylgruppe, eine Phenylgruppe, eine substituierte Phenylgruppe,
R_{20} -H oder Halogen ist, und
R_{21} -H, niederes Alkyl, substituiertes niederes Alkyl, niederes Acyl oder substituiertes niederes Acyl ist, wobei die Bezeichnung "niederes Alkyl" eine C1-C20 geradkettige oder verzweigte Alkylgruppe betrifft, oder eine C3-C8 cyclische Alkylgruppe, und die Bezeichnungen "niederes Alkoxy", "niederes Acyl", "(niederes Alkoxy)Methyl" und "(niederes Alkyl)Thiomethyl" -O-(niederes Alkyl), -C(O)-(niederes Alkyl), -CH_2-(niederes Alkyl) bzw. -CH_2-S-(niederes Alkyl) bedeuten und die Bezeichnungen "substituiertes niederes Alkoxy" und "substituiertes niederes Acyl" -O-(substituiertes niederes Alkyl) bzw. -C(O)-(substituiertes niederes Alkyl) bedeuten.

24. Die Verwendung gemäß Anspruch 23, wobei
R_{10} Phenyl, tert-Butoxy, -S-CH_2-CH-$(CH_3)_2$, -S-$CH(CH_3)_3$, -S-$(CH_2)_3CH_3$, -O-$CH(CH_3)_3$, -NH-$CH(CH_3)_3$, -CH=C$(CH_3)_2$ oder para-Chlorphenyl ist,
R_{11} Phenyl, $(CH_3)_2CHCH_2$-, -2-Furanyl, Cyclopropyl oder para-Toluyl ist,
R_{12} -H, -OH, CH_3CO- oder -$(CH_2)_2$-N-Morpholino ist,
R_{13} Methyl ist oder R_{13} und R_{14} zusammengenommen -CH_2- sind,
R_{14} -H, -CH_2SCH_3 oder -CH_2-O-P(O)$(OH)_2$ ist,
R_{15} CH_3CO- ist,
R_{16} Phenyl ist,
R_{17} -H ist oder R_{17} und R_{18} zusammen genommen -O-CO-O- sind,
R_{18} -H ist,
R_{20} -H oder -F ist, und
R_{21} -H, -C(O)-CHBr-$(CH_2)_{13}$-CH_3 oder -C(O)-$(CH_2)_{14}$-CH_3, -C(O)-CH_2-CH(OH)-COOH, -C(O)-CH_2-O-C(O)-CH_2CH(NH_2)-$CONH_2$, -C(O)-CH_2-O-$CH_2CH_2OCH_3$ oder -C(O)-O-C(O)-CH_2CH_3 ist.

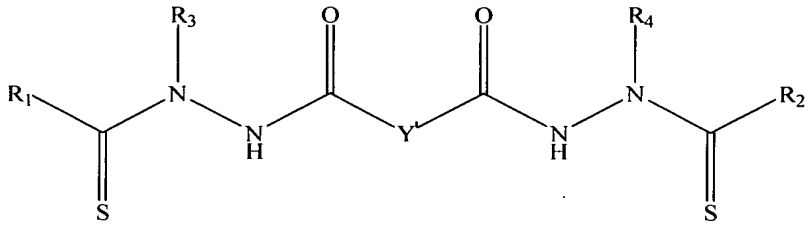
25. Die Verwendung gemäß Anspruch 22, wobei ein Taxolanaloges in dem Medikament enthalten ist, wobei das Taxolanaloge repräsentiert wird durch eine Struktur, wie sie in jeder der Figuren 5 - 25 gezeigt ist, wobei das Taxolanaloge das Copolymere aus N-(2-Hydroxypropyl)-methacrylamid, Methacryloylglycin-2-hydroxypropylamid und [2aR[2α,4β,4β,6β,9α(2R,3S),11β,12α,12α,12α]]-6,12b-diacetoxy-9-[3-benzamido-2-(methacryloyl-glycycl-L-phenylalanyl-L-leucylglycyloxy)-3-phenylpropionyloxy]-12-benzoyloxy-4,11 -dihydroxy-4a,8,13,13-tetramethyl-2a, 3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benz[1,2-b]oxet-5-on ist, oder dem Proband Taxol oder Taxoter verabreicht wird.

26. Die Verwendung gemäß Anspruch 23, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y' eine kovalente Bindung ist oder $-CR_7R_8-$.

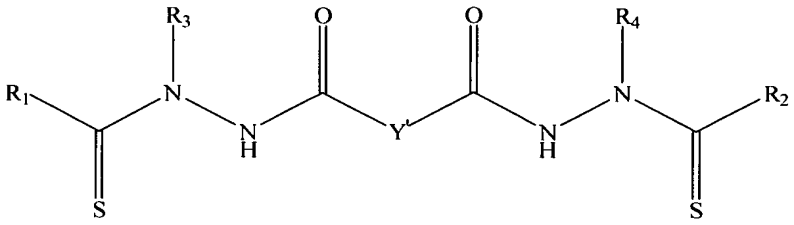
27. Die Verwendung gemäß Anspruch 23, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



wobei Y' eine kovalente Bindung ist oder $-CR_7R_8$.

28. Die Verwendung gemäß Anspruch 27, wobei R_1 und R_2 beide Aryl- oder substituierte Arylgruppen sind und R_3 und R_4 beide eine C1-C20 geradkettige oder verzweigte Alkylgruppe sind, oder eine C3-C8 cyclische Alkylgruppe oder eine substituierte C1-C20 geradkettige oder verzweigte Alkylgruppe oder eine C3-C8 cyclische Alkylgruppe.

29. Verwendung einer Verbindung, repräsentiert durch die folgende Strukturformel:



oder ein physiologisch akzeptables Salz davon, wobei:

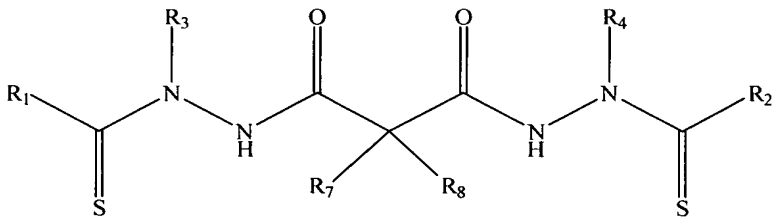
Y' eine kovalente Bindung ist oder $-CR_7R_8-$,
R_1 und R_2 beide eine substituierte oder unsubstituierte Arylgruppe sind,
R_3 und R_4 beide -H, Methyl oder Ethyl sind und
R_7 -H ist und R_8 -H oder Methyl ist,

für die Herstellung eines Medikaments, um die Antikrebsaktivität von Taxol oder einem Taxolanalogen zu erhöhen.

30. Die Verwendung gemäß Anspruch 29, wobei R_1 und R_2 beide Phenyl sind, wahlweise substituiert mit einer oder mehreren Gruppen, ausgewählt aus -OH, -Br, -Cl, -J, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$,

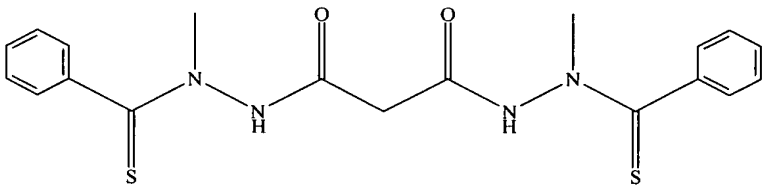
-NHR^a, -$N(R^aR^b)$, -$COOR^a$, -CHO, -$CONH_2$, -$CONHR^a$, -$CON(R^aR^b)$, -$NHCOR^a$, -$NRCOR^a$, -$NHCONH_2$, -$NHCONR^aH$, -$NHCON(R^aR^b)$, -NR^cCONH_2, -NR^cCONR^aH, -$NR^cCON(R^aR^b)$, -$C(=NH)-NH_2$, -$C(=NH)-NHR^a$, -$C(=NH)-N(R^aR^b)$, -$C(=NR^c)-NH_2$, -$C(=NR^c)-NHR^a$, -$C(=NR^c)-N(R^aR^b)$, -$NH-C(=NH)-NH_2$, -$NH-C(=NH)-NHR^a$, -$NH-C(=NH)-N(R^aR^b)$, -$NH-C(=NR^c)-NH_2$, -$NH-C(=NR^c)-NHR^a$, -$NH-C(=NR^c)-N(R^aR^b)$, -$NR^dH-C(=NH)-NH_2$, -$NR^d-C(=NH)-NHR^a$, -$NR^d-C(=NH)-N(R^aR^b)$, -$NR^d-C(=NR^c)-NH_2$, -$NR^d-C(=NR^c)-NHR^a$, -$NR^d-C(=NR^c)-N(R^aR^b)$, -$NHNH_2$, -$NHNHR^a$, -NHR^aR^b, -SO_2NH_2, -SO_2NHR^a, -$SO_2NR^aR^b$, -$CH=CHR^a$, -$CH=CR^aR^b$, -$CR^c=CR^aR^b$, -$CR^c=CHR^a$ -$CR^c=CR^aR^b$, -CCR^a, -SH, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, Alkylgruppe, nicht-aromatischer heterocyclischer Gruppe, Benzylgruppe oder Arylgruppe, wobei R^a-R^d jeweils unabhängig voneinander eine Alkylgruppe, Benzyl- oder aromatische Gruppe sind, oder -NR^aR^d zusammen genommen auch eine unsubstituierte nicht-aromatische heterocyclische Gruppe bilden können.

31. Verwendung einer Verbindung, repräsentiert durch die folgende Strukturformel:



oder eines physiologisch akzeptablen Salzes davon, wobei R_1 und R_2 beides Phenyl sind, R_3 und R_4 beides Methyl sind, R_7 und R_8 beide -H sind,
für die Herstellung eines Medikaments, um die Antikrebsaktivität von Taxol oder einem Taxolanalogen zu verbessern.

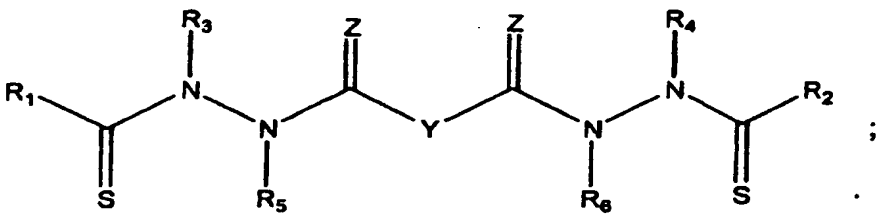
32. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung repräsentiert wird durch die folgende Strukturformel:



oder ein physiologisch akzeptables Salz davon.

Revendications

1. Composé représenté par la formule structurale suivante :

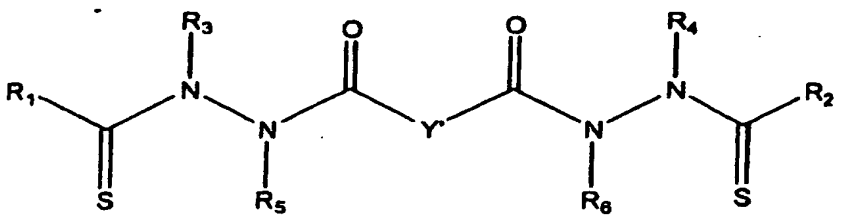


;

ou sel pharmaceutiquement acceptable de celui-ci, où :

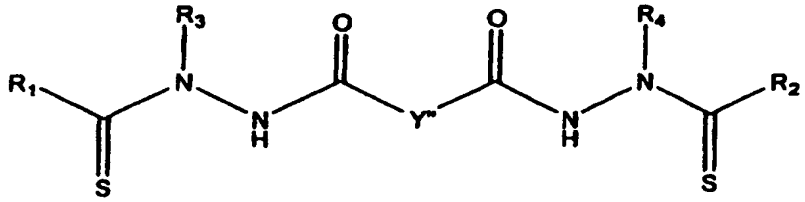
Y est une liaison covalente ou un groupe hydrocarbyle linéaire substitué ou non substitué ;
R_1 et R_2 sont indépendamment un groupe aryle ou un groupe aryle substitué ;
R_3 et R_4 sont indépendamment -H, un groupe aliphatique, un groupe aliphatique substitué, un groupe aryle ou un groupe aryle substitué ;
R_5 - R_6 sont indépendamment -H ou un groupe aliphatique ; et
Z est =O ou =S ;
à condition que, quand Y est $-CH_2-$, R_3 et R_4 sont l'un et l'autre phényle et R_5 - R_6 sont tous -H, R_1 et R_2 ne soient pas l'un et l'autre phényle.

2. Composé selon la revendication 1 où le composé est représenté par la formule structurale suivante :



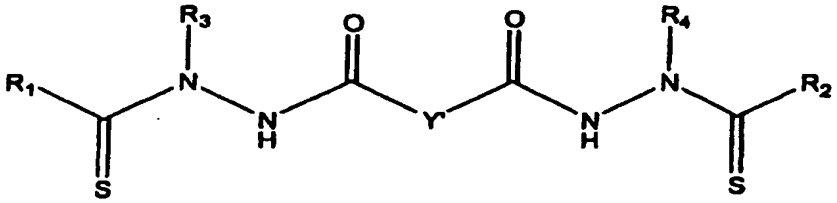
où Y' est une liaison covalente ou $-CR_7R_8-$ et R_7 et R_8 sont chacun indépendamment -H, un groupe aliphatique ou aliphatique substitué, ou R_7 est -H et R_8 est un groupe aryle substitué ou non substitué, ou, R_7 et R_8, pris ensemble, sont un groupe C2-C6 alkylène substitué ou non substitué.

3. Composé selon la revendication 2 où le composé est représenté par la formule structurale suivante :



où Y" est une liaison covalente ou $-CH_2-$.

4. Composé selon la revendication 2 où le composé est représenté par la formule structurale suivante :



où Y' est une liaison covalente ou $-CR_7R_8-$.

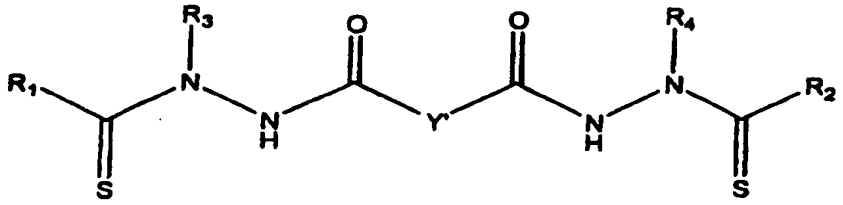
5. Composé selon la revendication 4 où R_1 et R_2 sont l'un et l'autre des groupes aryle ou aryle substitués et R_3 et R_4 sont l'un et l'autre un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique ou un groupe

C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique.

6. Composé selon la revendication 5 où R_1 et R_2 sont l'un et l'autre phényle ou phényle substitué et R_3 et R_4 sont l'un et l'autre méthyle, éthyle, phényle ou thiényle.

7. Composé selon la revendication 6 où R_7 et R_8 sont l'un et l'autre méthyle ou bien où R_7 et R_8 , pris ensemble, sont propylène ou butylènes, ou bien R_7 est -H et R_8 est alkyle inférieur, thiényle, phényle ou benzyle.

8. Composé selon la revendication 1 représenté par la formule structurale suivante :



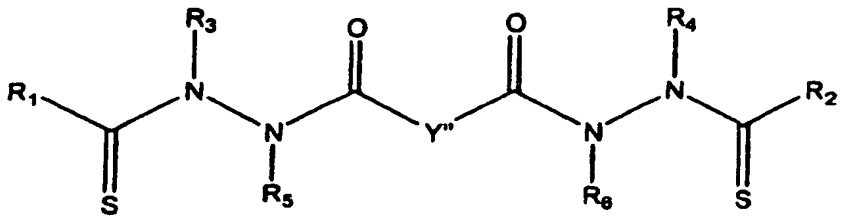
;

ou sel physiologiquement acceptable de celui-ci, où :

Y' est une liaison covalente ou $-CR_7R_8-$;
R_1 et R_2 sont l'un et l'autre un groupe aryle substitué ou non substitué ;
R_3 et R_4 sont l'un et l'autre -H, méthyle ou éthyle ; et
R_7 est -H et R_8 est -H ou méthyle.

9. Composé selon la revendication 8 où R_1 et R_2 sont l'un et l'autre phényle éventuellement substitué avec un ou plusieurs groupes choisis parmi -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCON-R^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, un groupe alkyle, un groupe hétérocyclique non aromatique, un groupe benzyle ou un groupe aryle où R^a-R^d sont chacun indépendamment un groupe alkyle, benzyle, ou un groupe aromatique, ou $-NR^aR^d$, pris ensemble, peuvent former aussi un groupe hétérocyclique non aromatique non substitué.

10. Composé selon la revendication 2 où le composé est représenté par la formule structurale suivante :



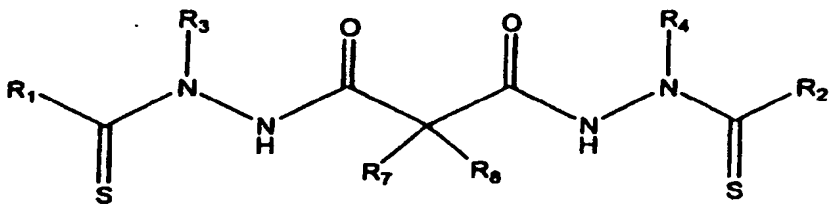
;

où Y" est une liaison covalente ou $-CH_2-$.

11. Composé selon la revendication 10 où R_5 et R_6 sont l'un et l'autre un groupe C1-C20 alkyle linéaire ou ramifié ou

un groupe C3-C8 alkyle cyclique ou un groupe phényle.

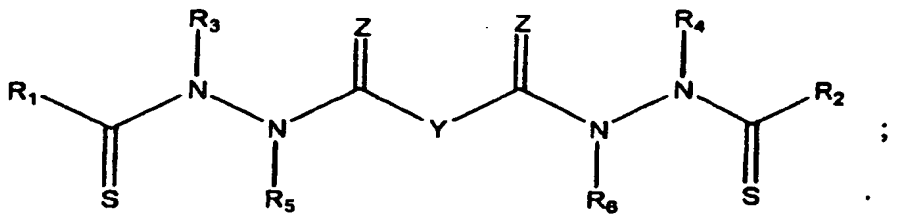
12. Composé selon la revendication 1 représenté par la formule structurale suivante :



ou sel physiologiquement acceptable de celui-ci, où

a) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
b) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre éthyle ; R_7 et R_8 sont l'un et l'autre -H ;
c) R_1 et R_2 sont l'un et l'autre 4-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
d) R_1 et R_2 sont l'un et l'autre 4-méthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
e) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
f) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre éthyle ; R_7 est méthyle ; R_8 est -H ;
g) R_1 et R_2 sont l'un et l'autre 4-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
h) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
i) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
j) R_1 et R_2 sont l'un et l'autre 3-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
k) R_1 et R_2 sont l'un et l'autre 3-fluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
l) R_1 et R_2 sont l'un et l'autre 4-chlorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
m) R_1 et R_2 sont l'un et l'autre 2-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
n) R_1 et R_2 sont l'un et l'autre 3-méthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
o) R_1 et R_2 sont l'un et l'autre 2,3-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
p) R_1 et R_2 sont l'un et l'autre 2,3-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
q) R_1 et R_2 sont l'un et l'autre 2,5-difluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
r) R_1 et R_2 sont l'un et l'autre 2,5-difluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
s) R_1 et R_2 sont l'un et l'autre 2,5-dichlorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
t) R_1 et R_2 sont l'un et l'autre 2,5-diméthylphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
u) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
v) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ; et
w) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;

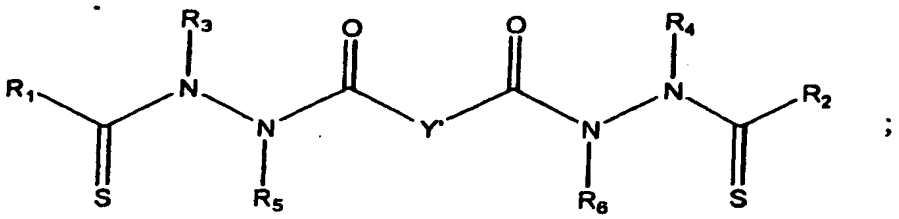
13. Composition pharmaceutique comprenant un support ou diluant pharmaceutiquement acceptable et un composé représenté par la formule structurale suivante :



ou un sel physiologiquement acceptable de celui-ci, où :

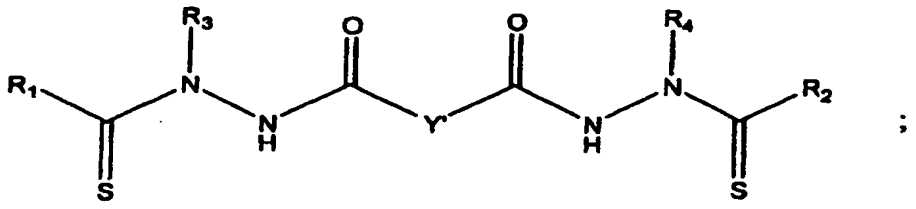
Y est une liaison covalente ou un groupe hydrocarbyle linéaire substitué ou non substitué ;
R_1 et R_2 sont indépendamment un groupe aryle ou un groupe aryle substitué ;
R_3 et R_4 sont indépendamment -H, un groupe aliphatique, un groupe aliphatique substitué, un groupe aryle ou un groupe aryle substitué ;
R_5 - R_6 sont indépendamment -H ou un groupe aliphatique ; et
Z est =O ou =S.

14. Composition pharmaceutique selon la revendication 13 où le composé est représenté par la formule structurale suivante :



où Y' est une liaison covalente ou $-CR_7R_8-$ et R_7 et R_8 sont chacun indépendamment -H, un groupe aliphatique ou aliphatique substitué, ou R_7 est -H et R_8 est un groupe aryle substitué ou non substitué, ou, R_7 et R_8, pris ensemble, sont un groupe C2-C6 alkylène substitué ou non substitué.

15. Composition pharmaceutique selon la revendication 14 où le composé est représenté par la formule structurale suivante :

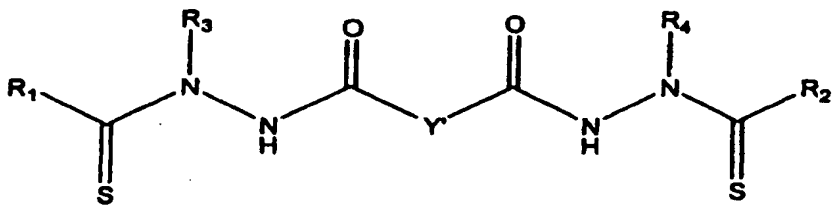


où Y' est une liaison covalente ou $-CR_7R_8-$.

16. Composition pharmaceutique selon la revendication 15 où R_1 et R_2 sont l'un et l'autre phényle ou phényle substitué ; R_3 et R_4 sont méthyle, éthyle, phényle ou thiényle ; et R_7 et R_8 sont l'un et l'autre méthyle ; R_7 et R_8, pris ensemble, sont propylène ou butylènes ; ou R_7 est -H et R_8 est alkyle inférieur, thiényle, phényle ou benzyle.

17. Composition pharmaceutique comprenant un support ou diluant pharmaceutiquement acceptable et un composé

représenté par la formule structurale suivante :

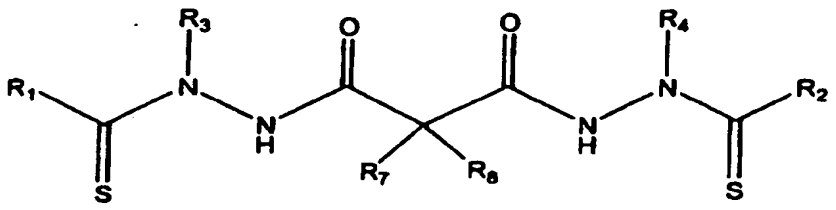


ou un sel physiologiquement acceptable de celui-ci, où :

Y' est une liaison covalente ou $-CR_7R_8-$;
R_1 et R_2 sont l'un et l'autre un groupe aryle substitué ou non substitué ;
R_3 et R_4 sont l'un et l'autre -H, méthyle ou éthyle ; et
R_7 est -H et R_8 est -H ou méthyle.

18. Composition pharmaceutique selon la revendication 17 où R_1 et R_2 sont l'un et l'autre phényle éventuellement substitué avec un ou plusieurs groupes choisis parmi -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR-CONR^aH$, $-NR^cCON(R^ak^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, les groupes alkyle, un groupe hétérocyclique non aromatique, un groupe benzyle ou un groupe aryle où R^a-R^d sont chacun indépendamment un groupe alkyle, benzyle, ou un groupe aromatique, ou $-NR^aR^d$, pris ensemble, peuvent former aussi un groupe hétérocyclique non aromatique non substitué.

19. Composition pharmaceutique comprenant un support ou diluant pharmaceutiquement acceptable et un composé représenté par la formule structurale suivante :

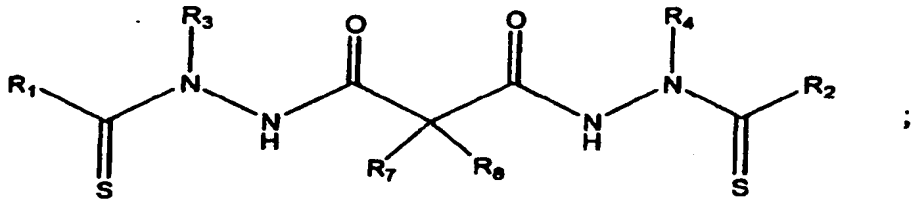


ou un sel physiologiquement acceptable de celui-ci, où

a) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
b) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre éthyle ; R_7 et R_8 sont l'un et l'autre -H ;
c) R_1 et R_2 sont l'un et l'autre 4-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
d) R_1 et R_2 sont l'un et l'autre 4-méthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
e) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
f) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre éthyle ; R_7 est méthyle ; R_8 est -H ;
g) R_1 et R_2 sont l'un et l'autre 4-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;

h) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
i) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
j) R_1 et R_2 sont l'un et l'autre 3-cyanophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
k) R_1 et R_2 sont l'un et l'autre 3-fluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
l) R_1 et R_2 sont l'un et l'autre 4-chlorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
m) R_1 et R_2 sont l'un et l'autre 2-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
n) R_1 et R_2 sont l'un et l'autre 3-méthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
o) R_1 et R_2 sont l'un et l'autre 2,3-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
p) R_1 et R_2 sont l'un et l'autre 2,3-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
q) R_1 et R_2 sont l'un et l'autre 2,5-difluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
r) R_1 et R_2 sont l'un et l'autre 2,5-difluorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H ;
s) R_1 et R_2 sont l'un et l'autre 2,5-dichlorophényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
t) R_1 et R_2 sont l'un et l'autre 2,5-diméthylphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
u) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ;
v) R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H ; et
w) R_1 et R_2 sont l'un et l'autre 2,5-diméthoxyphényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 est méthyle ; R_8 est -H.

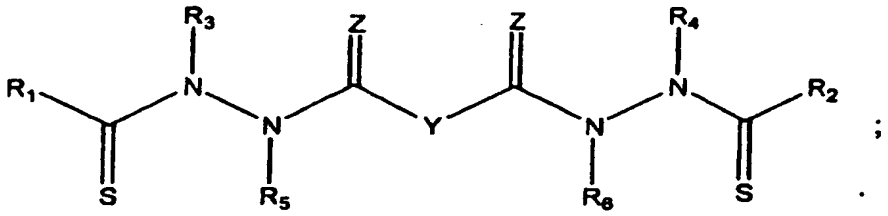
20. Composition pharmaceutique comprenant un support ou diluant pharmaceutiquement acceptable et un composé représenté par la formule structurale suivante :



;

où R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H.

21. Utilisation d'un composé représenté par la formule structurale suivante :

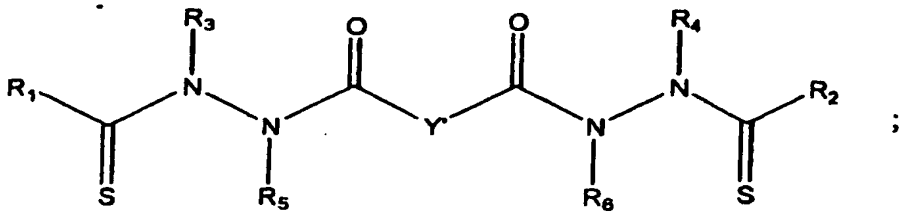


;

ou d'un sel physiologiquement acceptable de celui-ci, où :

Y est une liaison covalente ou un groupe hydrocarbyle substitué ou non substitué ;
R_1 et R_2 sont indépendamment un groupe aryle ou un groupe aryle substitué ;
R_3 et R_4 sont indépendamment -H, un groupe aliphatique, un groupe aliphatique substitué, un groupe aryle ou un groupe aryle substitué ;
R_5 - R_6 sont indépendamment -H ou un groupe aliphatique ;
et Z est =O ou =S,
pour la production d'un médicament pour augmenter l'activité anticancéreuse du taxol ou d'un analogue du taxol.

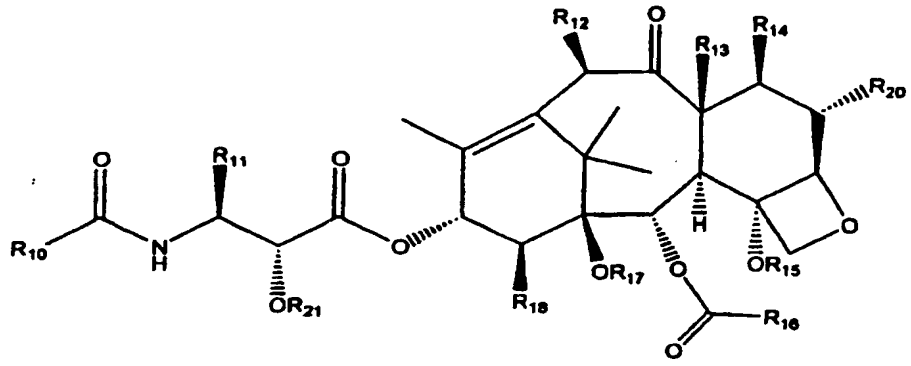
22. Utilisation selon la revendication 21 où le composé est représenté par la formule structurale suivante :



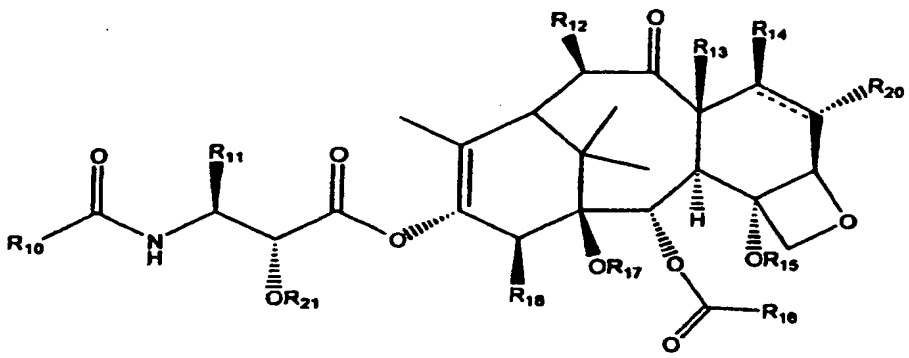
;

où Y' est une liaison covalente ou $-CR_7R_8-$ et R_7 et R_8 sont chacun indépendamment -H, un groupe aliphatique ou aliphatique substitué, ou R_7 est -H et R_8 est un groupe aryle substitué ou non substitué, ou, R_7 et R_8, pris ensemble, sont un groupe C2-C6 alkylène substitué ou non substitué.

23. Utilisation selon la revendication 22 où l'analogue du taxol est représenté par une formule structurale choisie parmi :



ou



où :

R_{10} est un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique, un groupe C1-C20 alkyle linéaire ou ramifié substitué ou un groupe C3-C8 alkyle cyclique, un groupe phényle, un groupe phényle substitué, $-SR_{19}$, $-NHR_{19}$ ou $-OR_{19}$;
R_{11} est un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique, un groupe C1-C20 alkyle linéaire ou ramifié substitué ou un groupe C3-C8 alkyle cyclique, un groupe aryle ou un groupe aryle substitué ;
R_{12} est -H, -OH, alkyle inférieur, alkyle inférieur substitué, alcoxy inférieur, alcoxy inférieur substitué, -O-C(O)-(alkyle inférieur), -O-C(O)-(alkyle inférieur substitué), $-O-CH_2-O-$(alkyle inférieur) $-S-CH_2-O-$(alkyle inférieur) ;
R_{13} est -H, $-CH_3$ ou, pris avec R_{14}, $-CH_2-$;
R_{14} est -H, -OH, alcoxy inférieur, -O-C(O)-(alkyle inférieur), alcoxy inférieur substitué, -O-C(O)-(alkyle inférieur substitué), $-O-CH_2-O-P(O)(OH)_2$, $-O-CH_2-O-$(alkyle inférieur), $-O-CH_2-S-$(alkyle inférieur) ou, pris avec R_{20}, une double liaison ;
R_{15} est -H, acyle inférieur, alkyle inférieur, alkyle inférieur substitué, alcoxyméthyle, alkylthiométhyle, -OC(O)-O(alkyle inférieur), -OC(O)-O(alkyle inférieur substitué), -OC(O)-NH(alkyle inférieur) ou -OC(O)-NH(alkyle inférieur substitué) ;
R_{16} est phényle ou phényle substitué ;
R_{17} est -H, acyle inférieur, acyle inférieur substitué, alkyle inférieur, alkyle inférieur substitué, (alcoxy inférieur)méthyle ou (alkyle inférieur)thiométhyle ;
R_{18} est -H, $-CH_3$ ou, pris avec R_{17} et les atomes de carbone auxquels R_{17} et R_{18} sont liés, un cycle hétérocyclique non aromatique à cinq ou six membres ;
R_{19} est un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique, un groupe C1-C20 alkyle linéaire ou ramifié substitué ou un groupe C3-C8 alkyle cyclique, un groupe phényle, un groupe phényle substitué ;
R_{20} est -H ou un halogène ; et
R_{21} est -H, alkyle inférieur, alkyle inférieur substitué, acyle inférieur ou acyle inférieur substitué, où le terme « alkyle inférieur » désigne un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique et les termes « alcoxy inférieur », « acyle inférieur », « (alcoxy inférieur)méthyle » et « (alkyle inférieur) thiométhyle » désignent -0-(alkyle inférieur), -C(O)-(alkyle inférieur), $-CH_2-$(alkyle inférieur) et $-CH_2-S-$(alkyle inférieur), respectivement, et les termes « alcoxy inférieur substitué » et « acyle inférieur substitué » désignent -O-(alkyle inférieur substitué) et -C(O)-(alkyle inférieur substitué), respectivement.

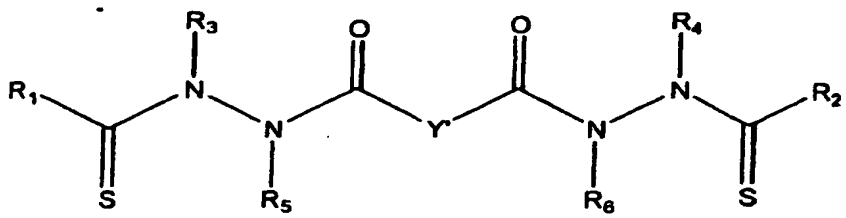
24. Utilisation selon la revendication 23 où :

R_{10} est phényle, *tert*-butoxy, $-S-CH_2-CH-(CH_3)_2$, $-S-CH(CH_3)_3$, $-S-(CH_2)_3CH_3$, $-O-CH(CH_3)_3$, $-NH-CH(CH_3)_3$, $-CH=C(CH_3)_2$ ou para-chlorophényle ;
R_{11} est phényle, $(CH_3)_2CHCH_2-$, -2-furanyle, cyclopropyle ou *para*-toluyle ;
R_{12} est -H, -OH, CH_3CO- ou $-(CH_2)_2-N$-morpholino ;
R_{13} est méthyle, ou R_{13} et R_{14}, pris ensemble, sont $-CH_2-$;
R_{14} est -H, $-CH_2SCH_3$ ou $-CH_2-O-P(O)(OH)_2$;

R_{15} est $-CH_3CO-$;
R_{16} est phényle ;
R_{17} est -H, ou R_{17} et R_{18}, pris ensemble, sont -O-CO-O- ;
R_{18} est -H ;
R_{20} est -H ou -F ; et
R_{21} est -H, $-C(O)-CHBr-(CH_2)_{13}-CH_3$ ou $-C(O)-(CH_2)_{14}-CH_3$; $-C(O)-CH_2-CH(OH)-COOH$, $-C(O)-CH_2-O-C(O)-CH_2CH(NH_2)-CONH_2$, $-C(O)-CH_2-O-CH_2CH_2OCH_3$ ou $-C(O)-O-C(O)-CH_2CH_3$.

25. Utilisation selon la revendication 22 où un analogue du taxol est compris dans le médicament l'analogue du taxol est représenté par une structure montrée dans l'une quelconque des figures 5-25, l'analogue du taxol est le copolymère de N-(2-hydroxypropyl)méthacrylamide, de méthacryloylglycine-2-hydroxypropylamide et de [2aR[2α,4β,4β,6β,9α(2R,3S),11β,12α,12α,12α]]-6,12b-diacétoxy-9-[3-benzamido-2-(méthacryloyl-glycyl-L-phénylalanyl-L-leucylglycyloxy)-3 -phénylpropionyloxy]-12-benzoyloxy-4,11-dihydroxy-4a, 8,13,13-tétraméthyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodécahydro-1H-7,11-méthanocyclodéca[3,4]benz[1,2-b]oxét-5-one, ou du taxol ou du taxotère est administré au sujet.

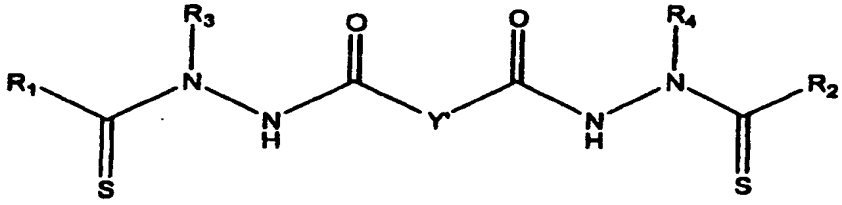
26. Utilisation selon la revendication 23 où le composé est représenté par la formule structurale suivante :



;

où Y' est une liaison covalente ou $-CR_7R_8-$.

27. Utilisation selon la revendication 23 où le composé est représenté par la formule structurale suivante :

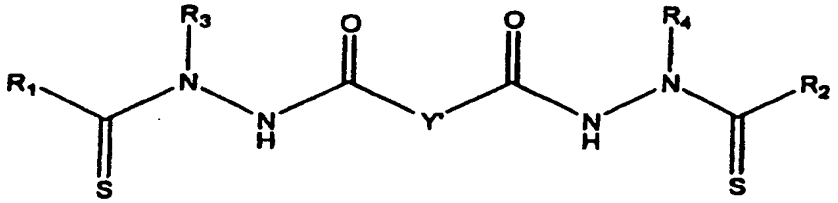


;

où Y' est une liaison covalente ou $-CR_7R_8-$.

28. Utilisation selon la revendication 27 où R_1 et R_2 sont l'un et l'autre des groupes aryle ou aryle substitués et R_3 et R_4 sont l'un et l'autre un groupe C1-C20 alkyle linéaire ou ramifié ou un groupe C3-C8 alkyle cyclique ou un groupe C1-C20 alkyle linéaire ou ramifié substitué ou un groupe C3-C8 cyclique.

29. Utilisation d'un composé représenté par la formule structurale suivante :

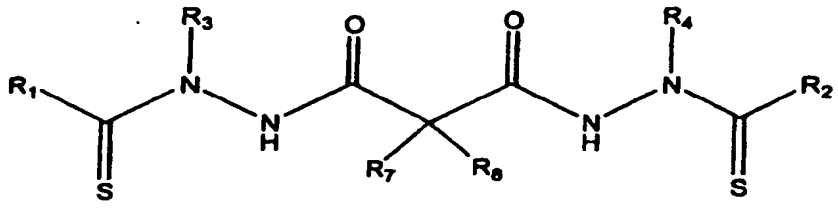


ou d'un sel physiologiquement acceptable de celui-ci, où :

Y' est une liaison covalente ou $-CR_7R_8-$;
R_1 et R_2 sont l'un et l'autre un groupe aryle substitué ou non substitué ;
R_3 et R_4 sont l'un et l'autre -H, méthyle ou éthyle ; et
R_7 est -H et R_8 est -H ou méthyle,
pour la production d'un médicament pour augmenter l'activité anticancéreuse du taxol ou d'un analogue du taxol.

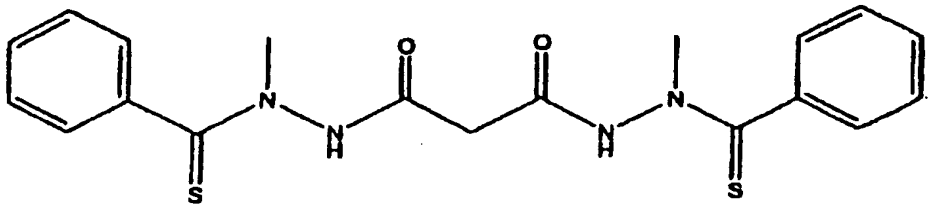
30. Utilisation selon la revendication 29 où R_1 et R_2 sont l'un et l'autre phényle éventuellement substitué avec un ou plusieurs groupes choisis parmi -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$ $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NRCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$ $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, les groupes alkyle, un groupe hétérocyclique non aromatique, un groupe benzyle ou un groupe aryle où R^a-R^d sont chacun indépendamment un groupe alkyle, benzyle, ou un groupe aromatique, ou $-NR^aR^d$, pris ensemble, peuvent former aussi un groupe hétérocyclique non aromatique non substitué.

31. Utilisation d'un composé représenté par la formule structurale suivante :



ou d'un sel physiologiquement acceptable de celui-ci, où R_1 et R_2 sont l'un et l'autre phényle ; R_3 et R_4 sont l'un et l'autre méthyle ; R_7 et R_8 sont l'un et l'autre -H,
pour la production d'un médicament pour augmenter l'activité anticancéreuse du taxol ou d'un analogue du taxol.

32. Composé selon la revendication 1 où le composé est représenté par la formule structurale suivante :



ou sel physiologiquement acceptable de celui-ci.

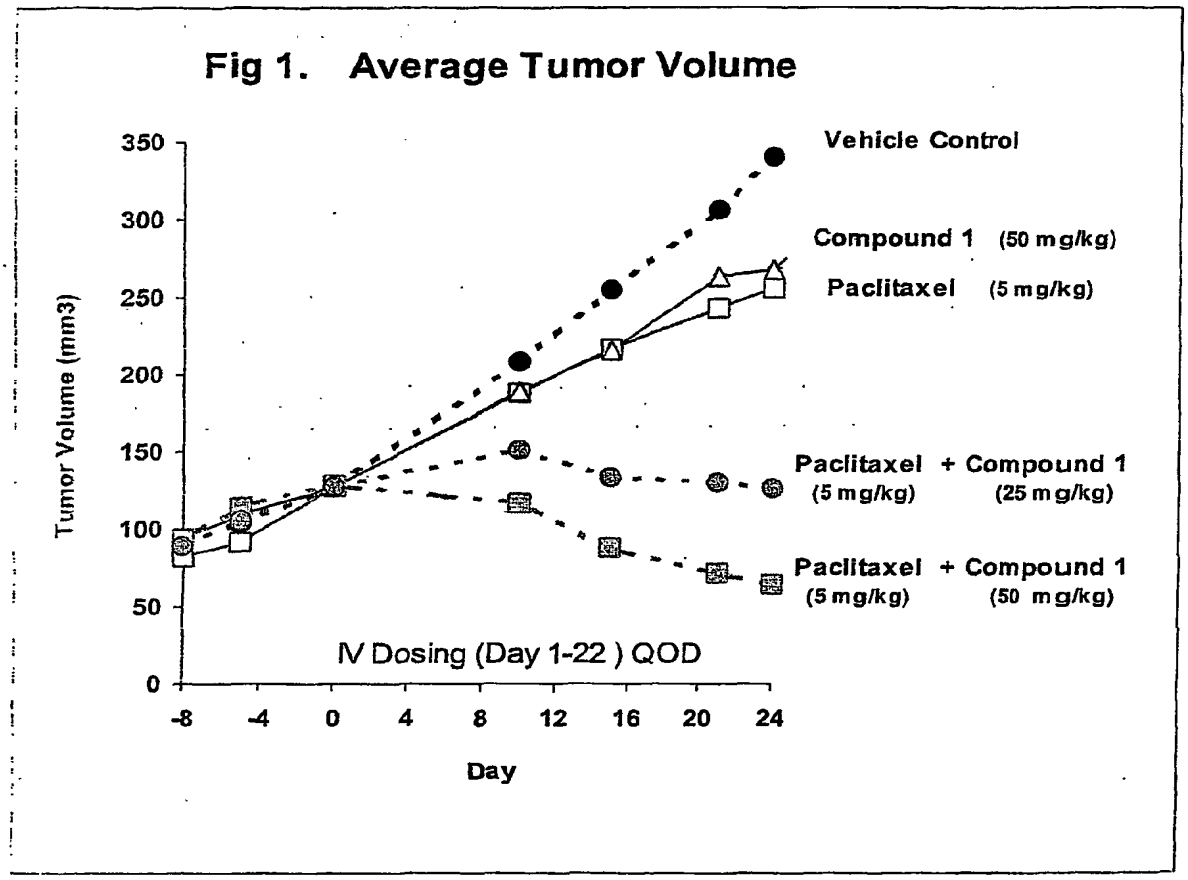


Fig 1. Average Tumor Volume
Tumor Volume (mm3)
350
300
250
200
150
100
50
0
-8
-4
0
4
8
12
16
20
24
Day
IV Dosing (Day 1-22) QOD
Vehicle Control
Compound 1 (50 mg/kg)
Paclitaxel (5 mg/kg)
Paclitaxel + Compound 1
(5 mg/kg) (25 mg/kg)
Paclitaxel + Compound 1
(5 mg/kg) (50 mg/kg)

Figure 1

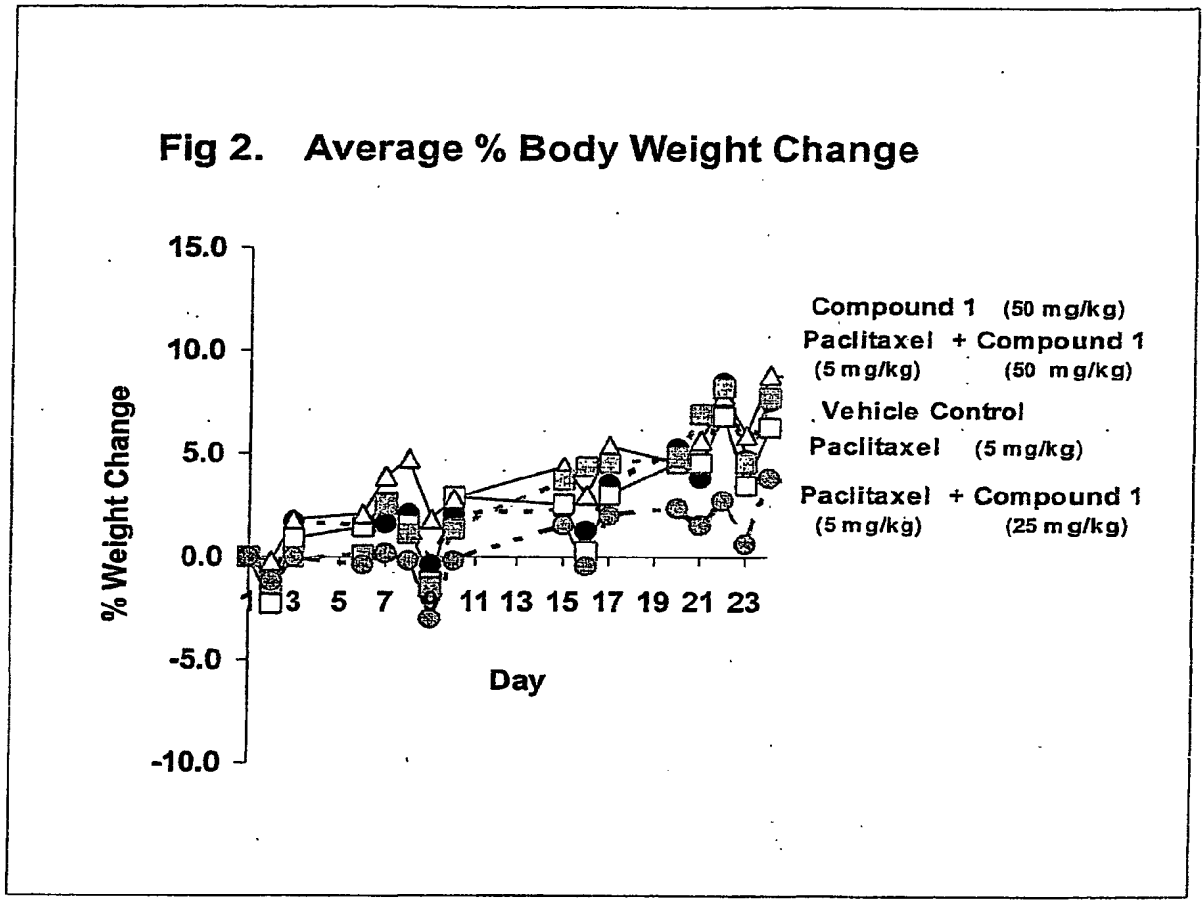


Fig 2. Average % Body Weight Change
15.0
10.0
5.0
0.0
-5.0
-10.0
% Weight Change
1 3 5 7 9 11 13 15 17 19 21 23
Day
Compound 1 (50 mg/kg)
Paclitaxel + Compound 1
(5 mg/kg) (50 mg/kg)
Vehicle Control
Paclitaxel (5 mg/kg)
Paclitaxel + Compound 1
(5 mg/kg) (25 mg/kg)

Figure 2

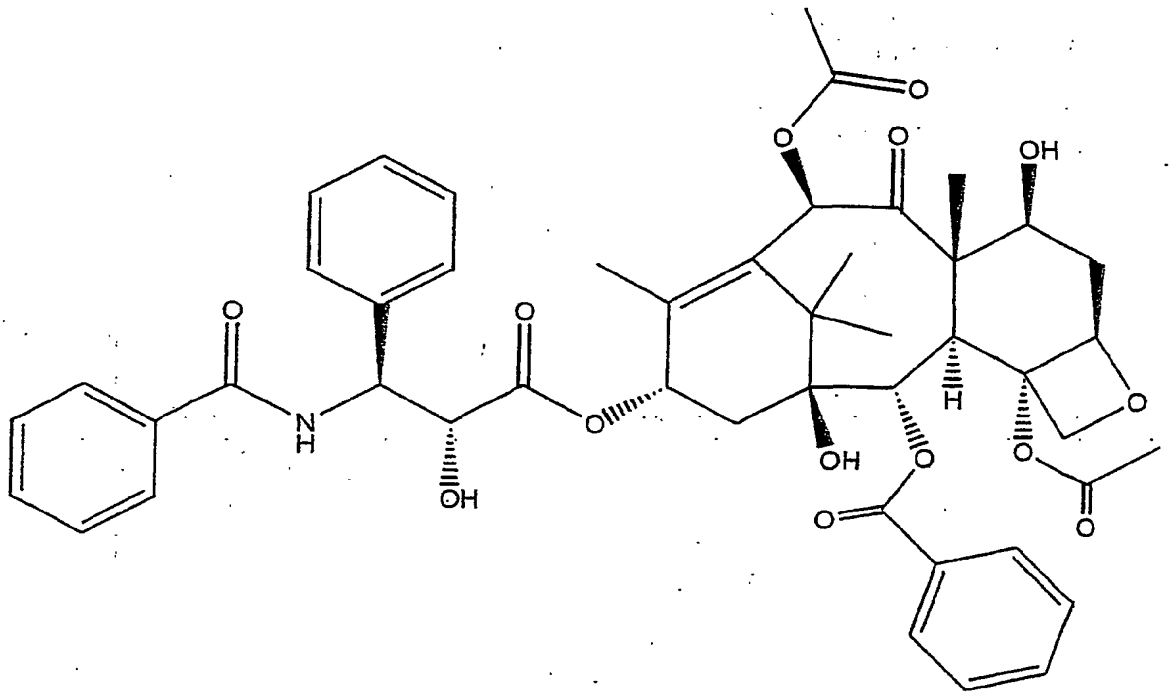


Figure 3

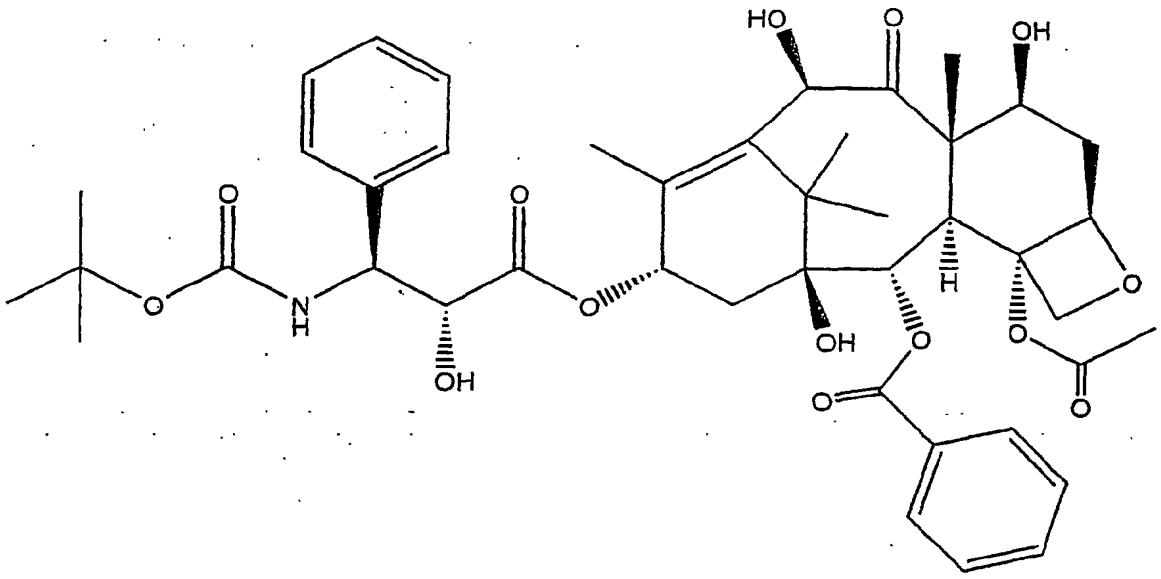


Figure 4

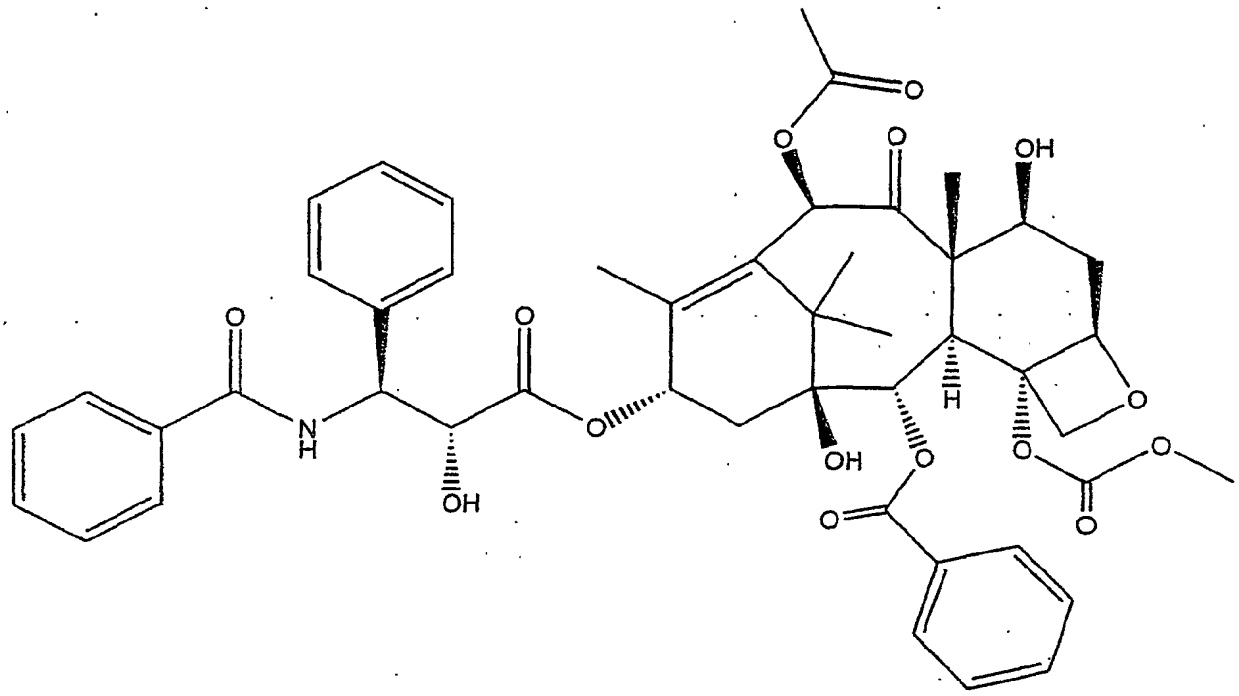


Figure 5

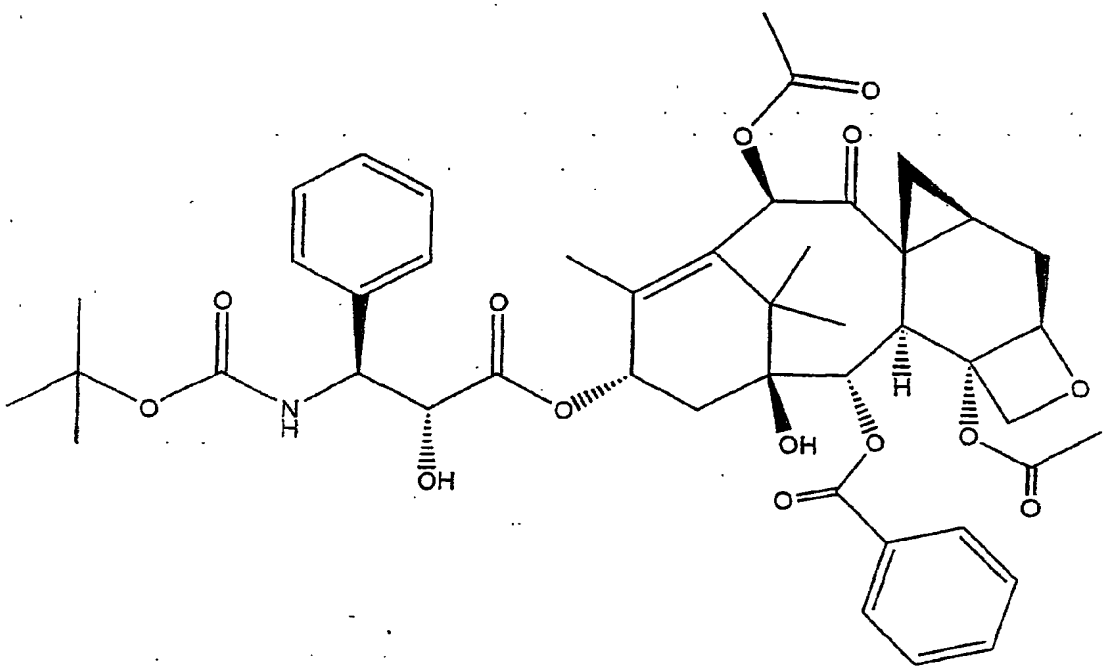


Figure 6

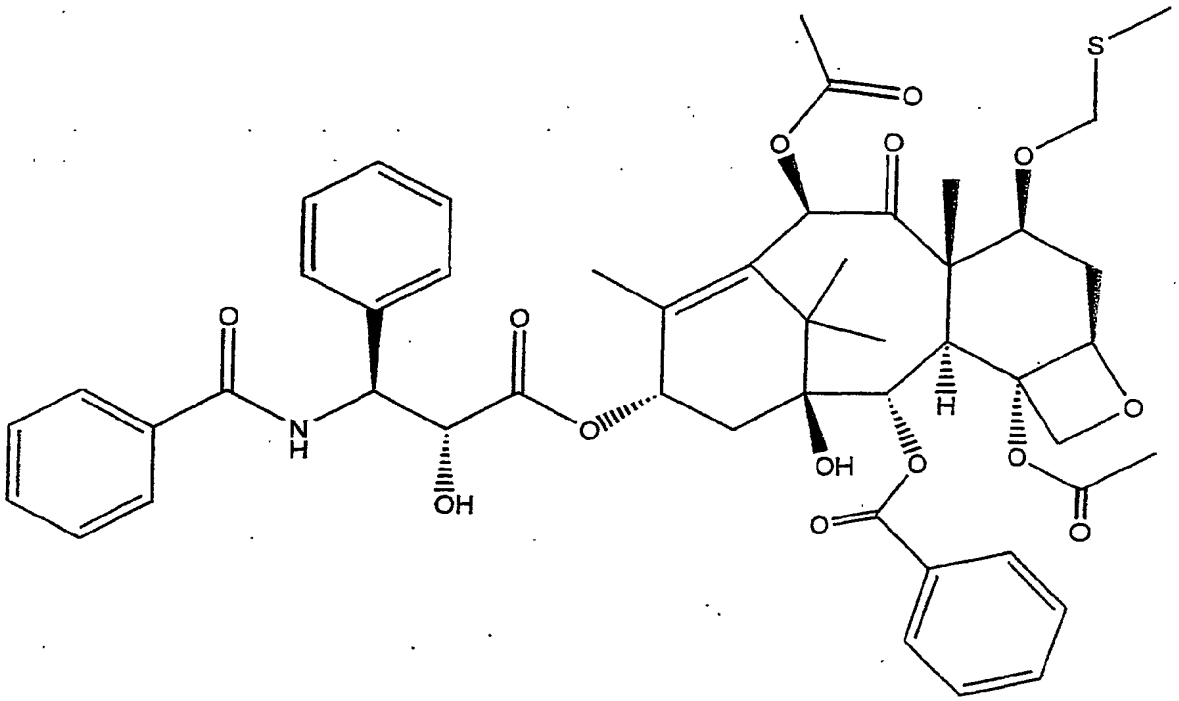


Figure 7

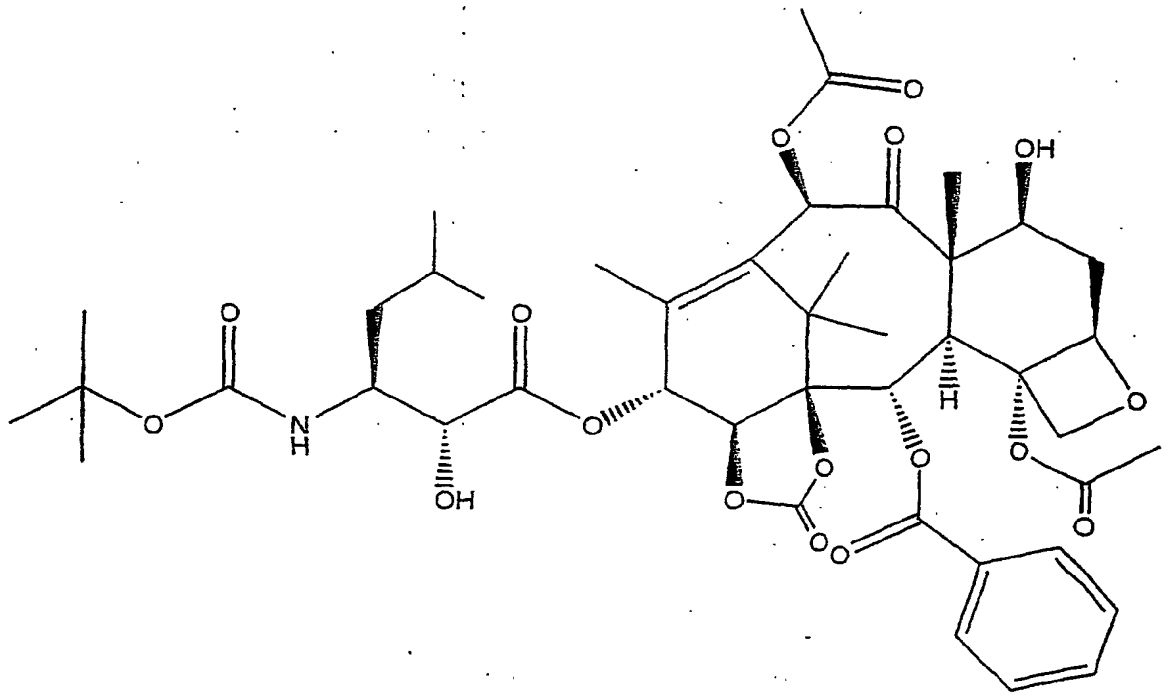


Figure 8

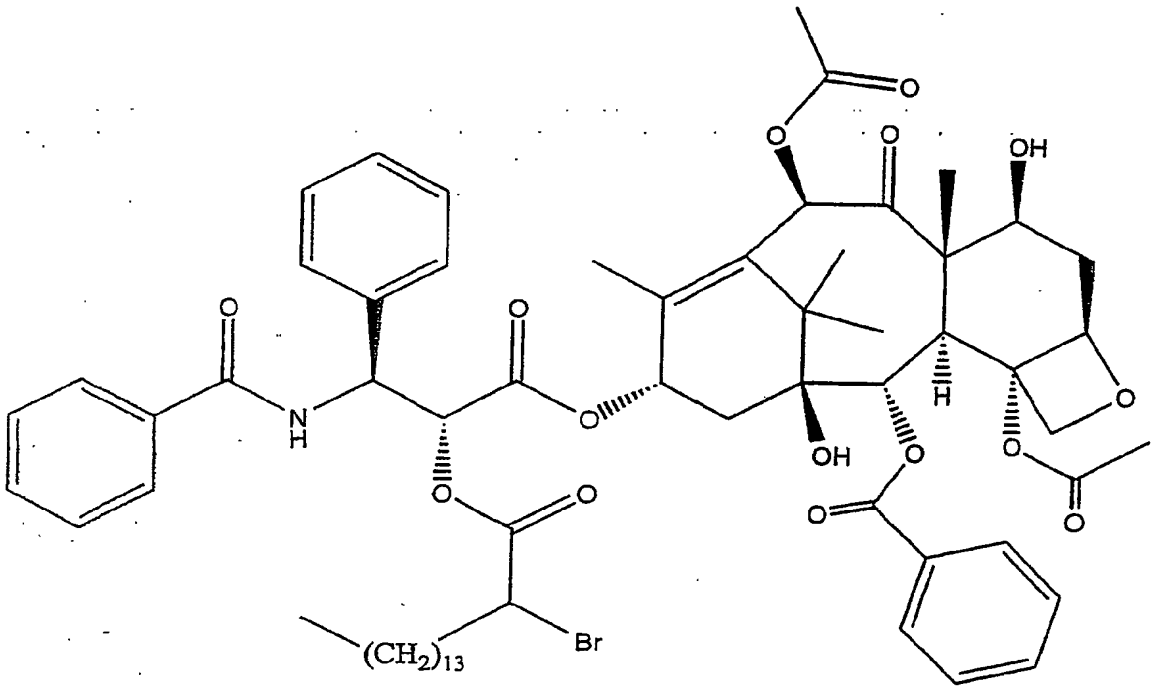


Figure 9

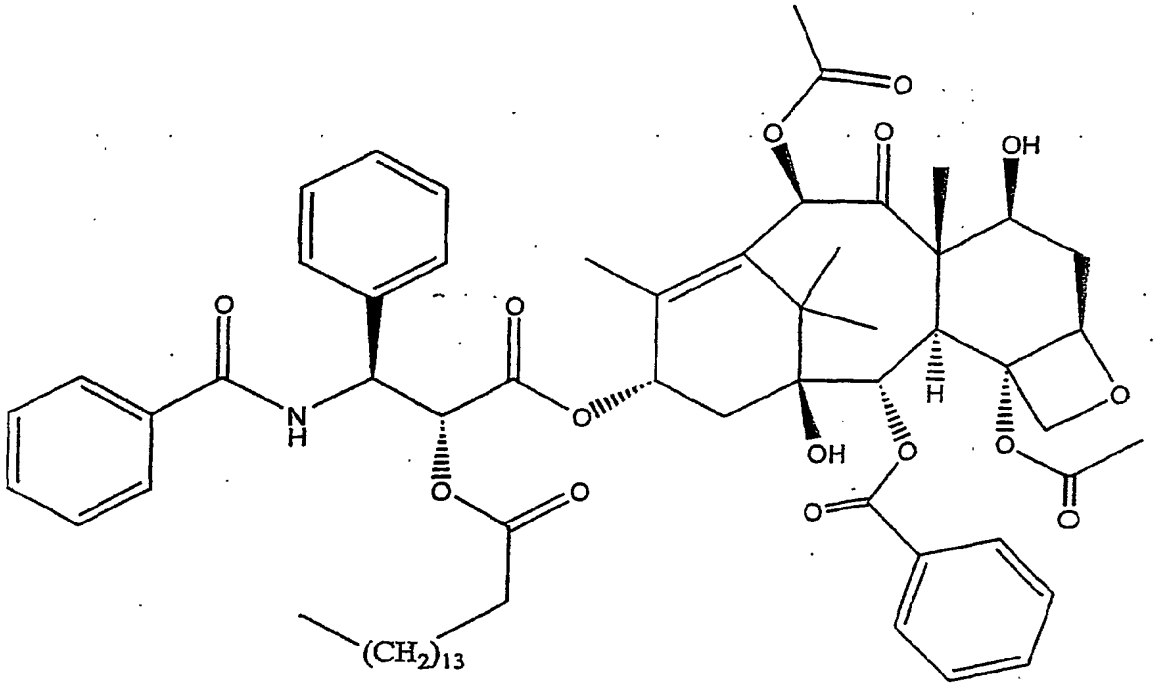


Figure 10

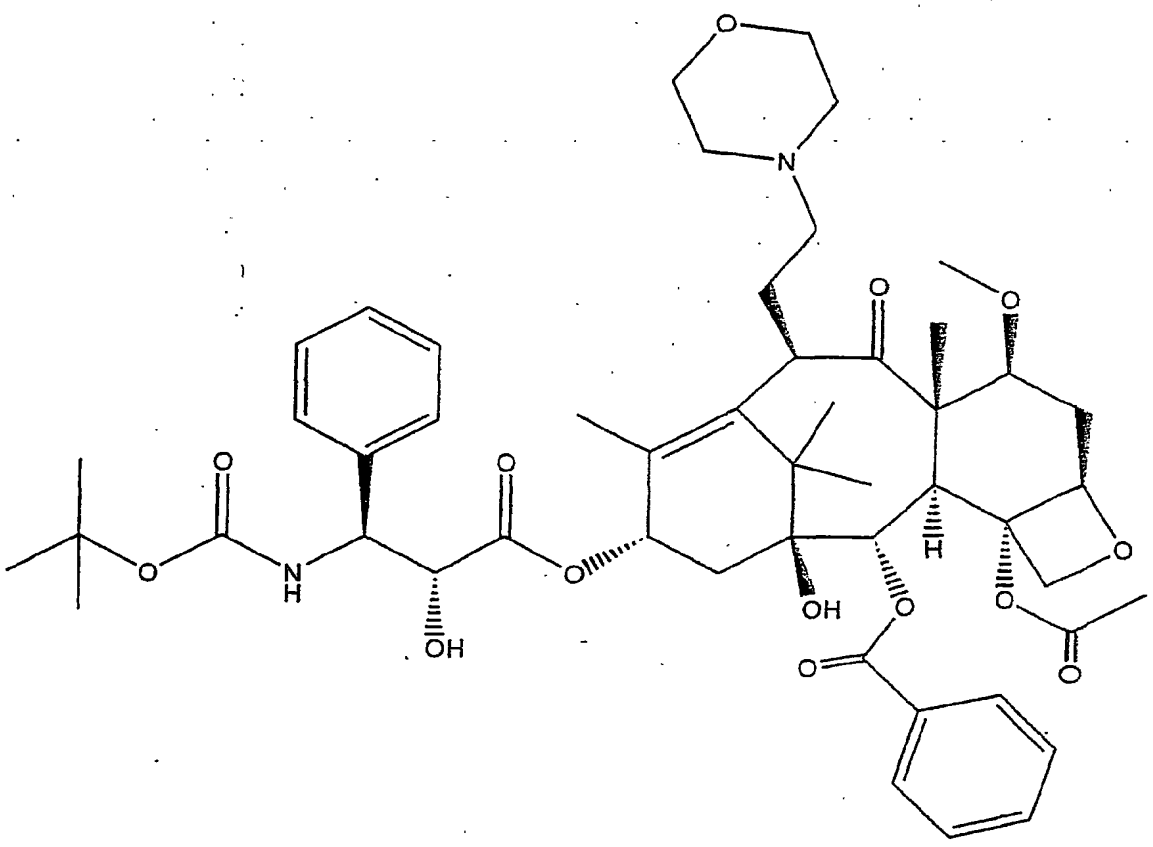


Figure 11

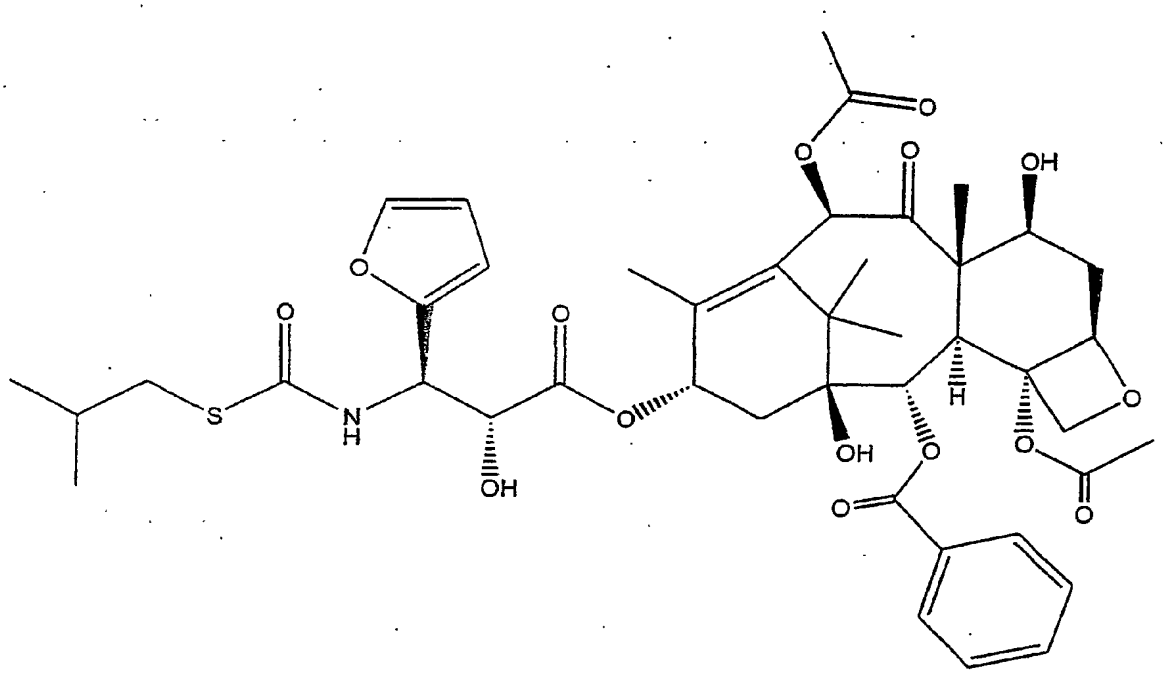


Figure 12

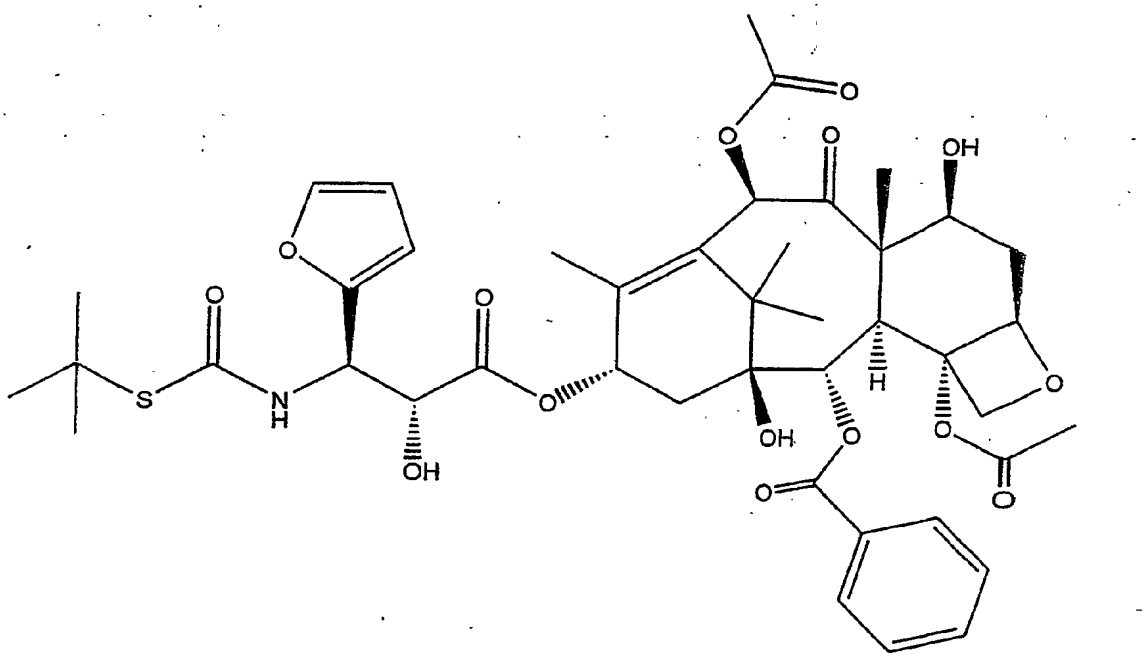


Figure 13

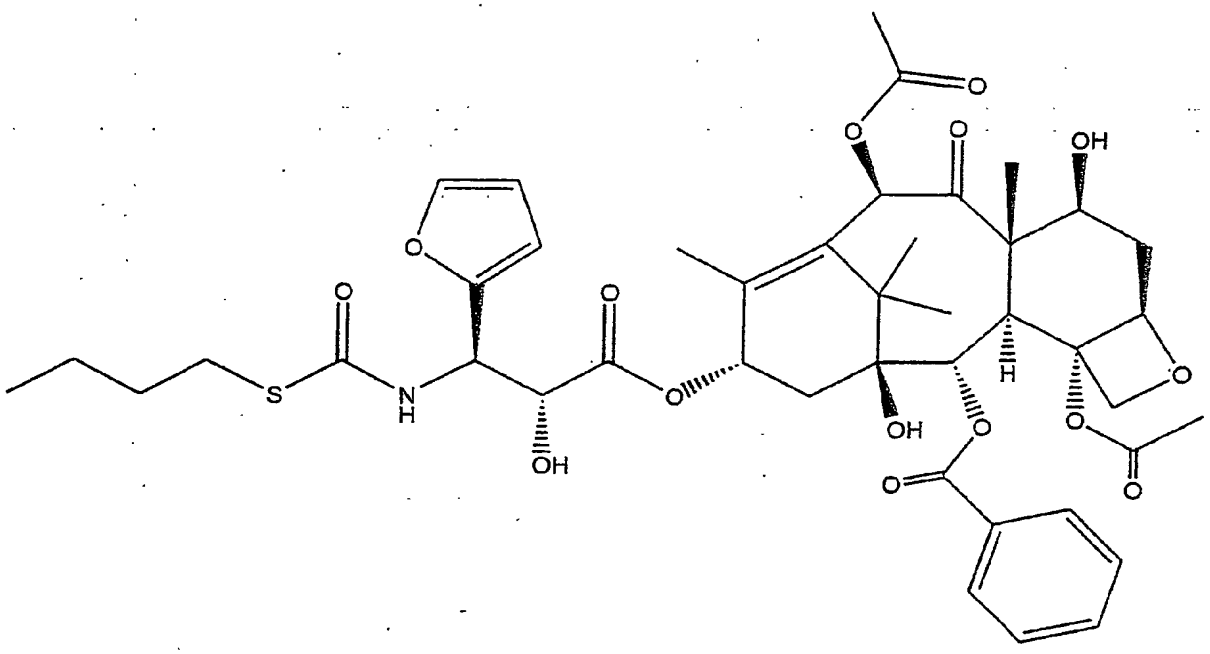


Figure 14

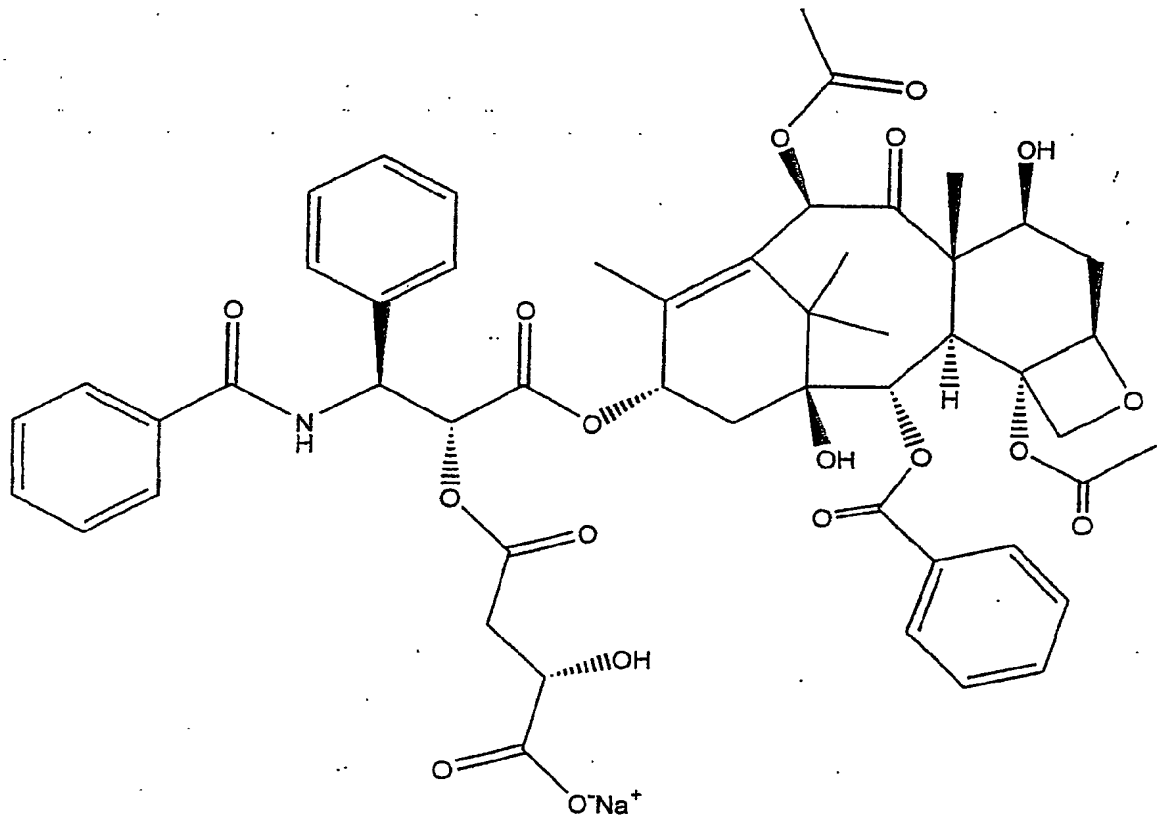


Figure 15

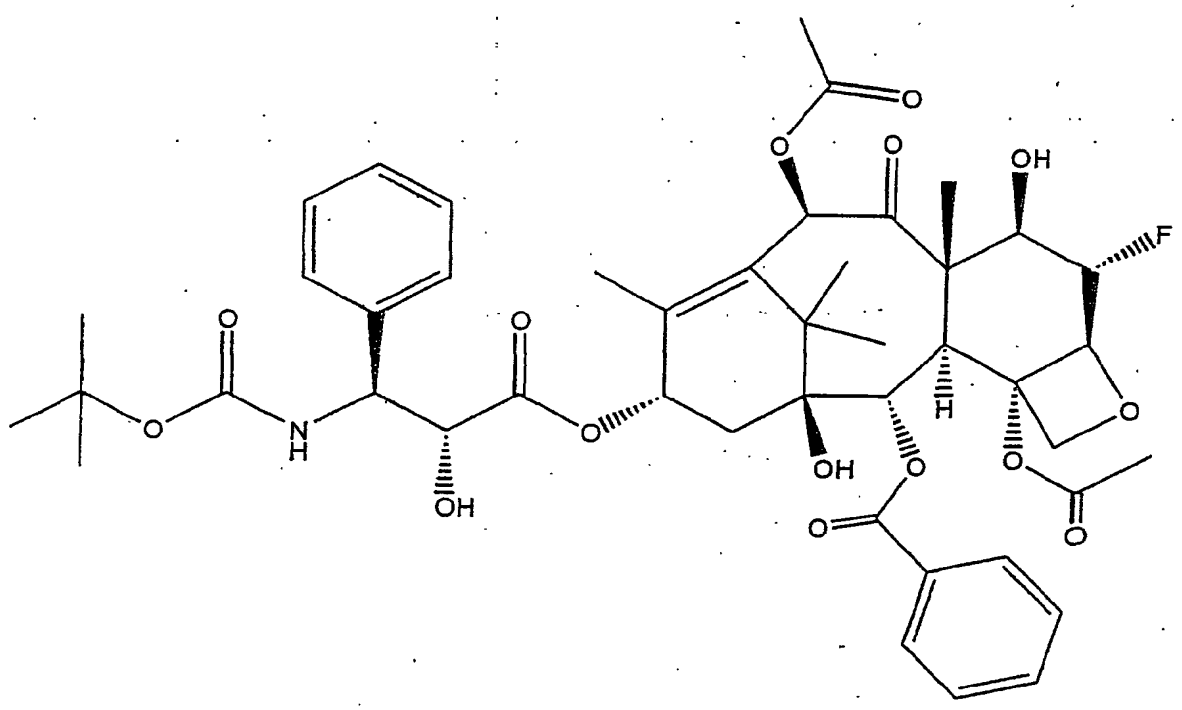


Figure 16

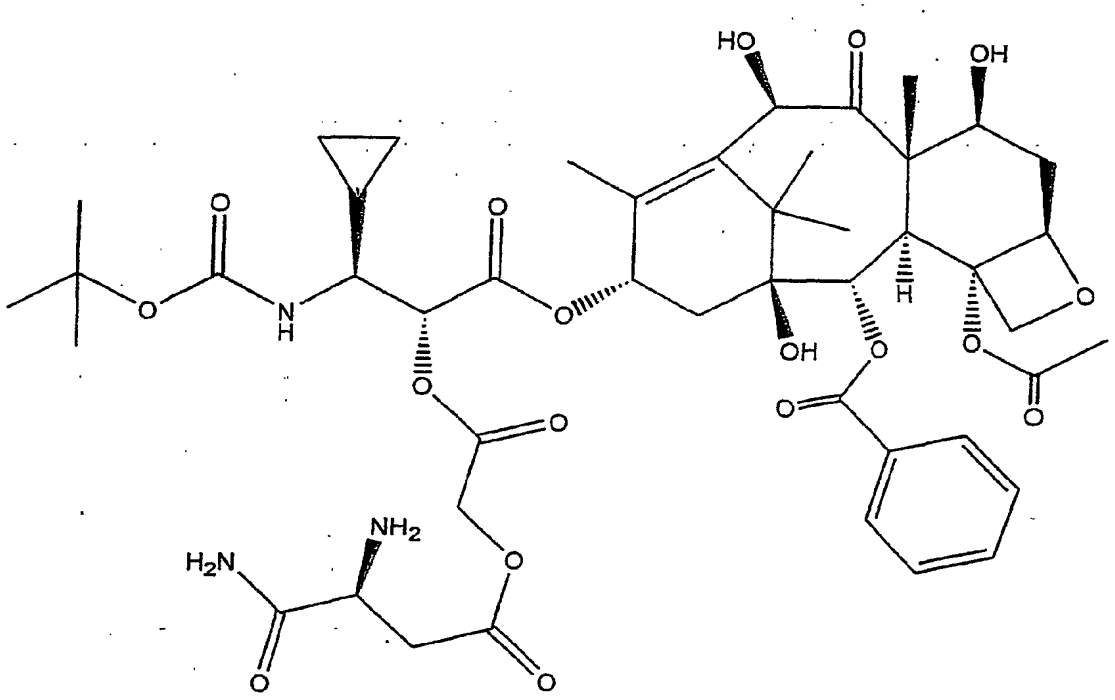


Figure 17

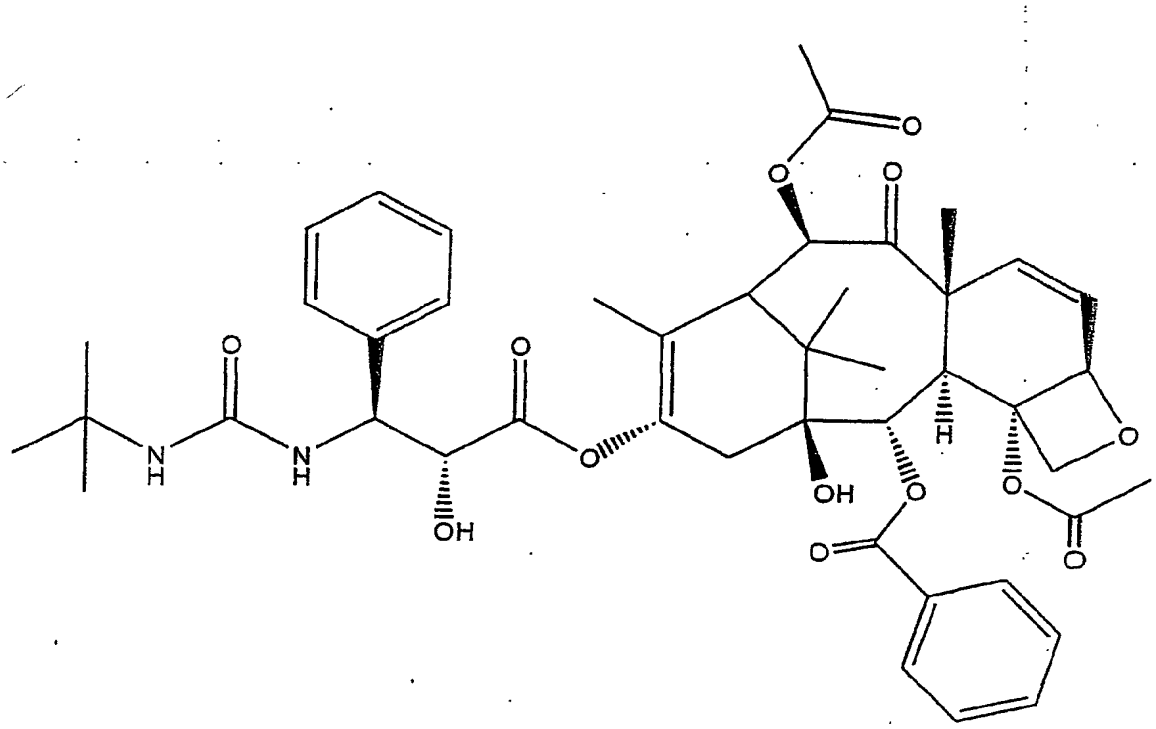


Figure 18

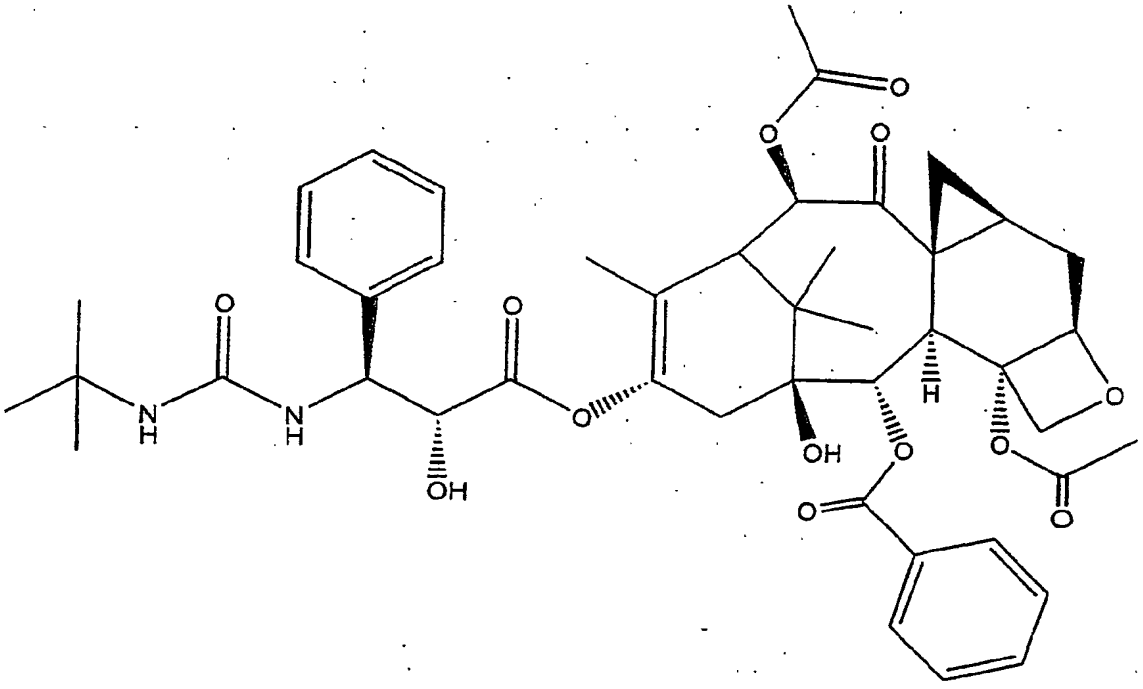


Figure 19

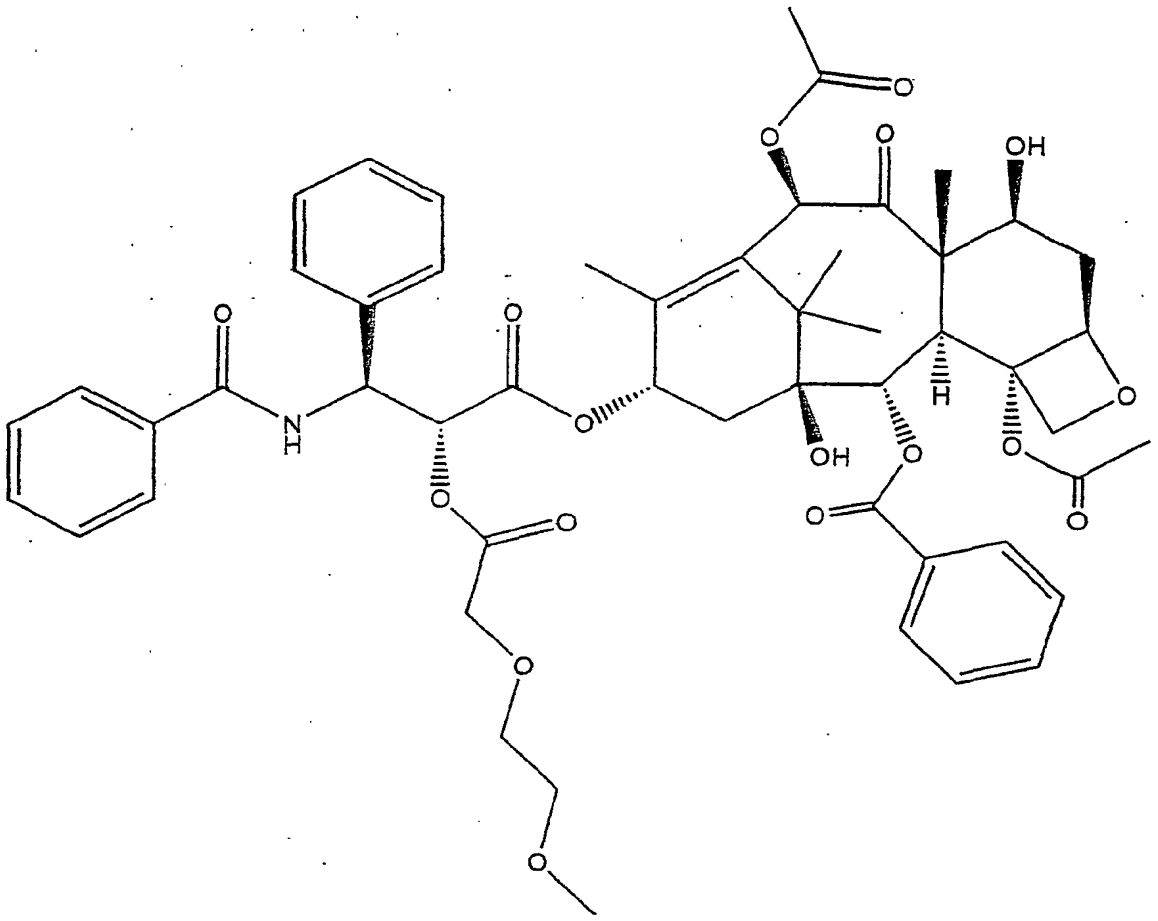


Figure 20

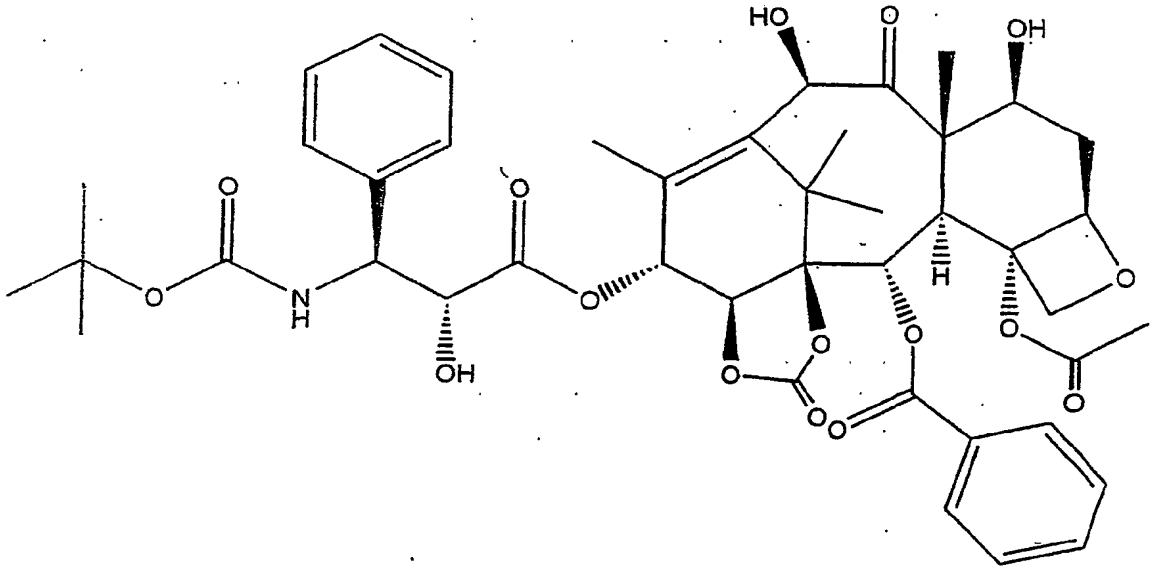


Figure 21

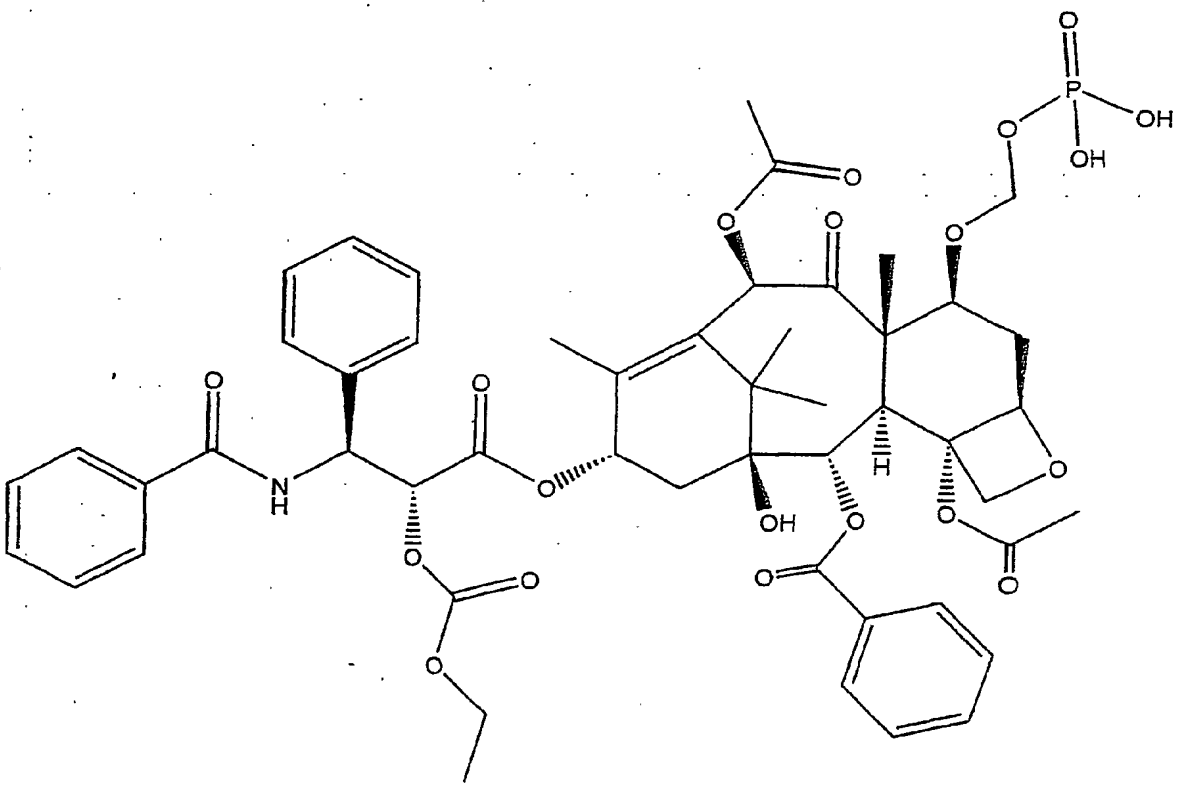


Figure 22

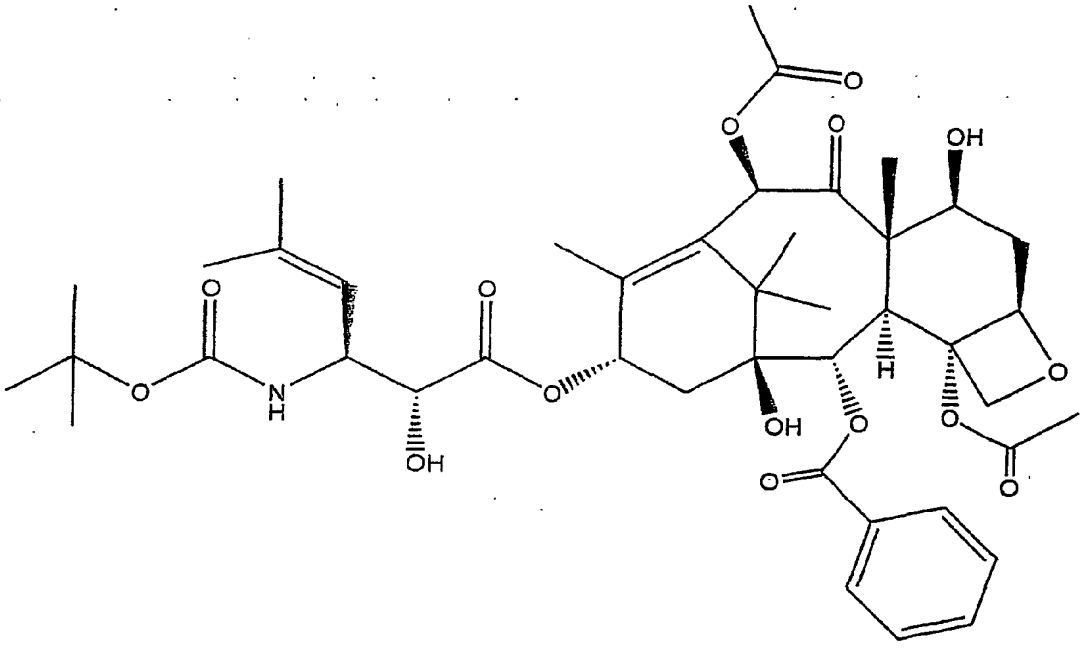


Figure 23

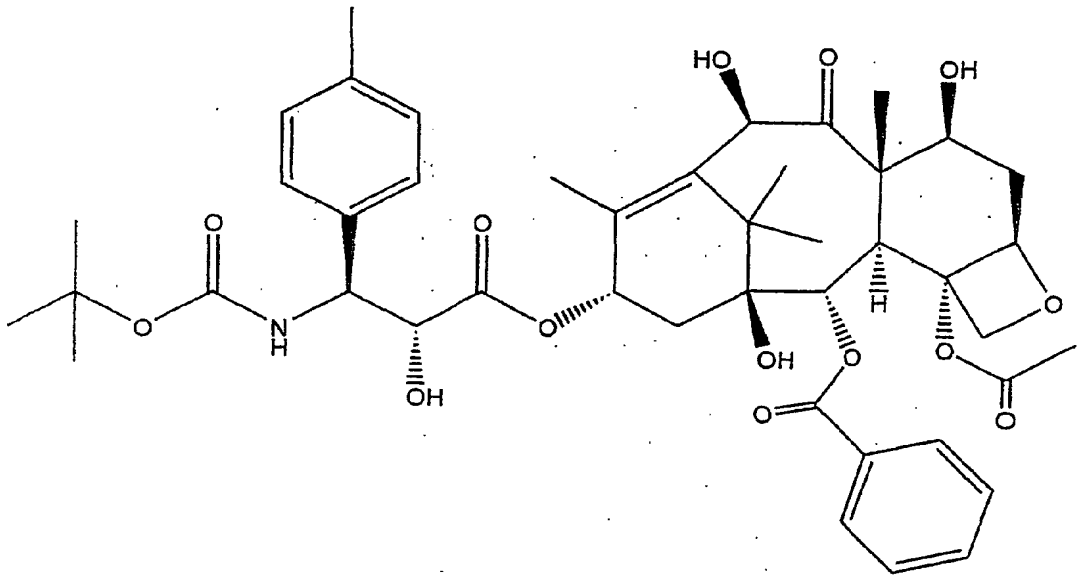


Figure 24

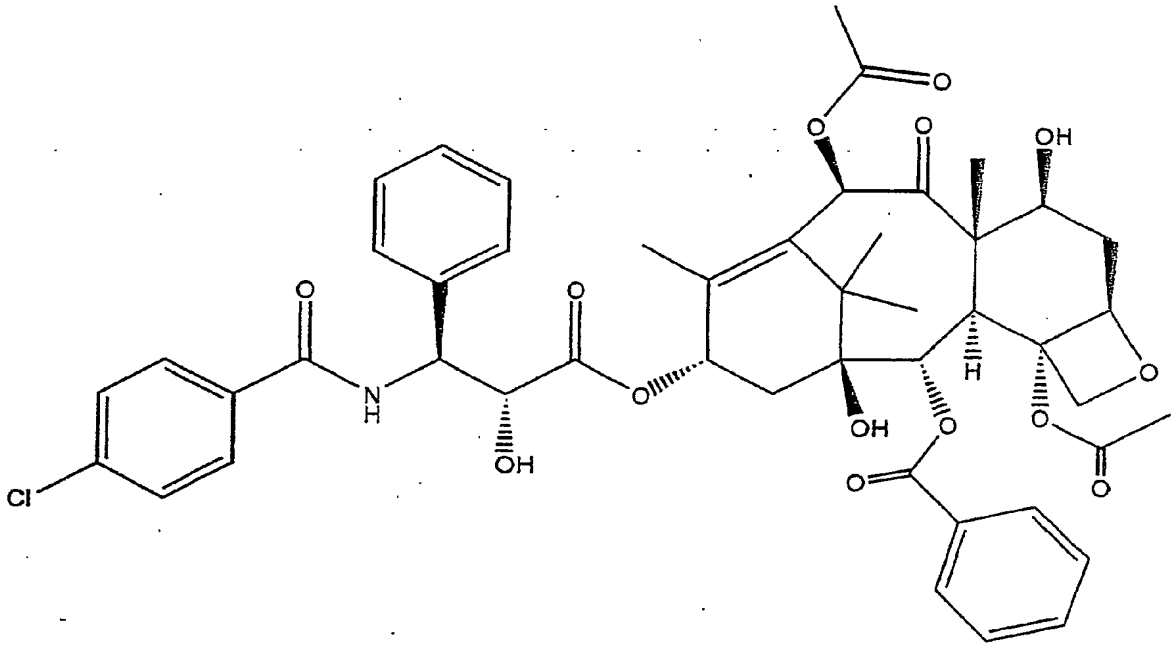


Figure 25

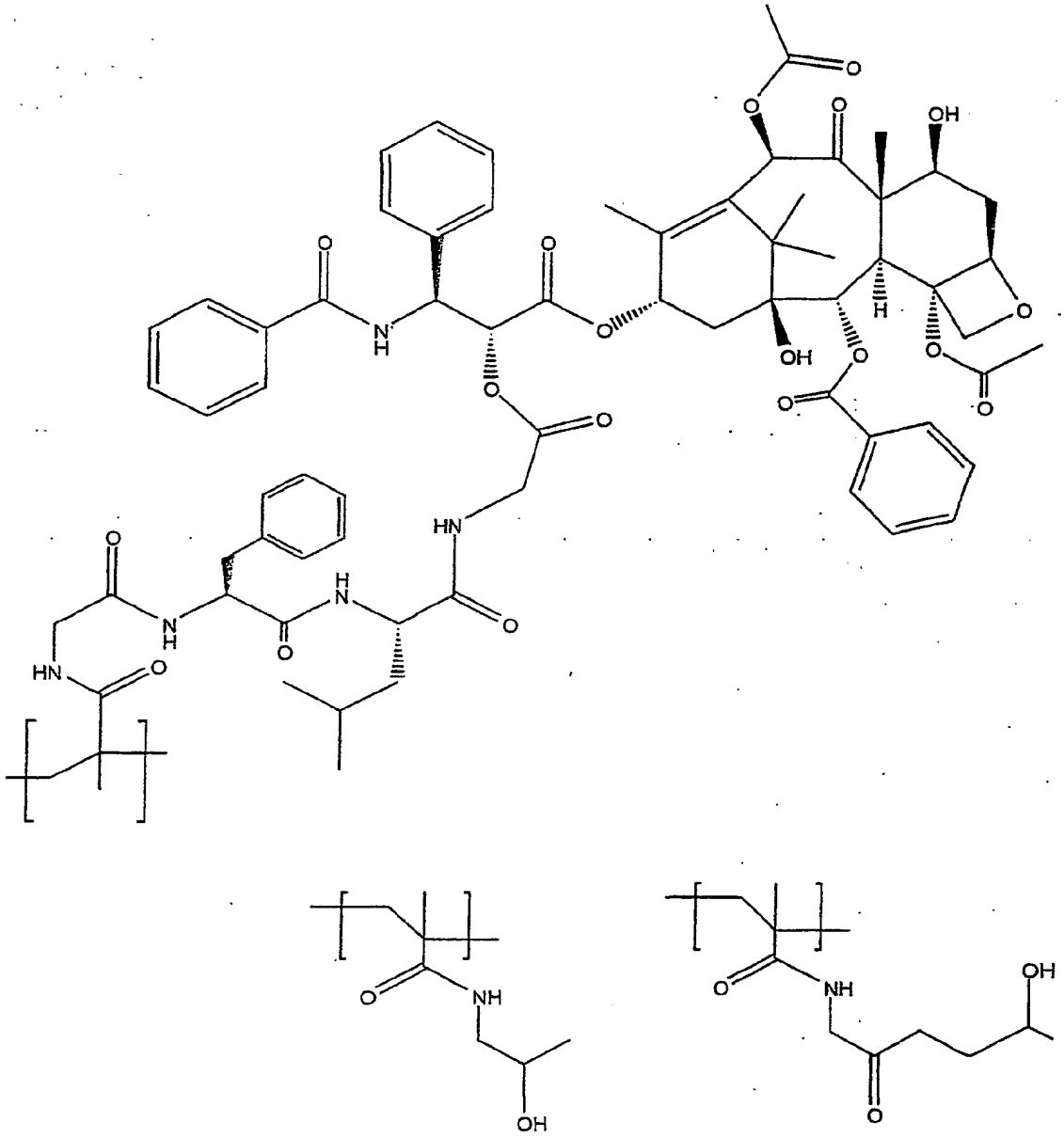


Figure 26